IO STATE
IVERSITY
JUL 25 1961
LIE

SHEFFIELD MEETING: JULY 17-22

# BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY JULY 8 1961

RECEIVED
JUL 27 1961
HEALTH CENTER LIBRARY

## TABLE OF CONTENTS

**Treatment of Schizophrenia in General Hospitals** PETER ROHDE, M.B., and WILLIAM SARGANT, F.R.C.P. ..... 67
**Anticoagulant Treatment in Progressing Stroke** A. BARHAM CARTER, M.D., F.R.C.P., D.P.M. ..... 70
**Survival after Non-haemorrhagic Cerebrovascular Accidents**
JOHN MARSHALL, M.D., F.R.C.P.Ed., M.R.C.P., D.P.M., and ANTHONY C. KAESER, M.B. ..... 73
**Management of Pulmonary Tuberculosis during Pregnancy**
RONALD B. PRIDIE, M.B., and PETER STRADLING, M.D., M.R.C.P. ..... 78
**Latent Brucellosis in Farmers** IAN MCWHINNEY, M.D., M.R.C.P., and A. P. PRIOR, M.B. ..... 80
**Incidence of Non-central Fixation in Children with Squint**
JOHN SCULLY, M.B., D.P.H., D.O.M.S., and E. J. NAYLOR, M.Sc.Tech., Ph.D. ..... 81
**Erythema Multiforme and Nephritis**
J. S. COMAISH, M.B., M.R.C.P., and D. N. S. KERR, M.B., M.Sc., M.R.C.P., M.R.C.P.Ed. ..... 84
**Chronic Bronchitis** P. O. LEGGAT, M.D., M.R.C.P., C. VERITY, M.D., D.P.H., and D. J. NEWELL, M.A. ..... 88
**Cryptococcal Meningo-encephalitis** W. F. TWINING MCMATH, M.D., M.R.C.P., D.P.H., and K. K. HUSSAIN, M.D. ..... 91
**Rapid Selection of Group A Recipients among Mass Casualties** P. D. STEWART, M.D., D.T.M.&H. ..... 93

**PRELIMINARY COMMUNICATIONS**
Small Doses of Intra-arterial $^{32}P$ in Location of Cerebral Tumours for Biopsy. LINDSAY SYMON, F.R.C.S., F.R.C.S.Ed. ..... 94

**MEDICAL MEMORANDA**
Cyanosis During Anaesthesia: An Unusual Case. W. SNIPER, M.B., F.F.A. R.C.S. ..... 96

**BOOK REVIEWS** ..... 97

**GENERAL ARTICLES AND NEWS**
To-day's Drugs ..... 107
NEW APPLIANCES ..... 106
OBITUARY ..... 115
MEDICAL NOTES IN PARLIAMENT ..... 119
VITAL STATISTICS ..... 121
MEDICAL NEWS ..... 123
BIRTHS, MARRIAGES, AND DEATHS ..... 124

**QUESTIONS AND COMMENTS**
Creaking Knees—Treatment of Stings—Duties of a Domiciliary Nurse—Prostatism—Purpura Associated with Thalidomide—Surgery for Chronic Glaucoma—Quarantine for Infective Hepatitis—Ribonucleic Acid Tablets—Treatment of Chloasma ..... 125–6

**LEADING ARTICLES**
Human Warehouses ..... 100
Latent Brucellosis ..... 101
Pulmonary Embolism ..... 101

**ANNOTATIONS**
Resuscitation of the Newborn by Cooling ..... 102
Experimental Glaucoma ..... 103
Medical Geography of Multiple Sclerosis 104
The Emotions and Electrolytes in Heart Failure ..... 104
Dr. Albert Schweitzer, HON.O.M. ..... 105

**CORRESPONDENCE**
Canvassing in Medical Elections. KENNEDY CASSELS, M.A. ..... 107
Barium Studies in the Aged. PAUL T. SAVAGE, F.R.C.S.; DAVID G. ILLINGWORTH, M.B. ..... 107
Antimony and the Heart. O. D. STANDEN, D.Sc. ..... 108

**SUPPLEMENT**
*Full Contents on First Page of Supplement*
Radiologists Group ..... 27
Pay in the Armed Forces ..... 28
Scottish News ..... 29
Correspondence:
Certificates for Light Work. W. P. KENNEDY, F.R.F.P.S. ..... 29

**CORRESPONDENCE**—*contd.*
Cataract and Steroids. H. BADERMAN, M.B., and C. MAGUIRE, M.B. ..... 108
Prevention of Rh Haemolytic Disease. R. FINN, M.R.C.P., and others ..... 109
Cortical Mastoidectomy. S. SILBERMANN, F.R.C.S. ..... 109
Geographical Pathology. A. JACOBS, M.D. ..... 109
Accident Neurosis. MICHAEL KELLY, M.D. ..... 110
Connubial Diabetes and the Possible Role of "Oral Diabetogens." M. E. DEUTSCH, Ph.D. ..... 110
Acute Diabetic Abdomen. R. PELLEGRINI, M.D. ..... 110
Dangers of Raw Milk. F. R. BROWN, F.R.C.S.Ed. ..... 111
Mortality from Primary Bone Tumours. C. H. G. PRICE, M.D. ..... 111
Noise in Hospital. DANIEL LAMONT, F.R.C.S.Ed. ..... 111
Oral Contraception. GABRIEL V. JAFFÉ, M.B. ..... 112
Pep Pill Merry-go-round. F. E. GRAHAM-BONNALIE, M.B. ..... 112
Prevention of Dental Caries. A. J. DALZELL-WARD, M.R.C.S. ..... 112
Collapse from Reserpine. K. D. SALZMANN, M.D. ..... 112
*Letters on other subjects on pp.* 113–115

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1

No. 5244, WEEKLY, PRICE 3/- Copyright © 1961 REGISTERED AS A NEWSPAPER

# STAPHYLOCOCCAL SUPERINFECTIONS

"Patients in hospital who have had an operation, and a course of 'broad—spectrum' antibiotics, sometimes develop diarrhoea which may be severe and even fatal."

*Lancet Annotations, 25th February, 1961*

## ENPAC

### LACTOBACILLUS ACIDOPHILUS PREPARATION

For the prophylaxis and treatment of staphylococcal super infections.

"It was found that the staphylococci increased in both groups at the beginning of antibiotic treatment. Staphylococci continued to increase in the patients taking the antibiotic alone, but in those taking 'ENPAC' there was a pronounced drop in numbers."

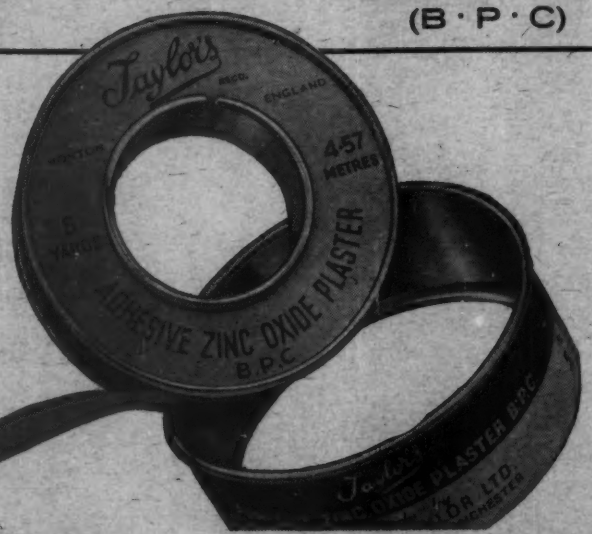
*Lancet—May 4th, 1957. pp. 899—901*

Samples and literature will be sent to the medical profession on request to:—

**WILTS UNITED DAIRIES LIMITED · NUTRITION DEPARTMENT · TROWBRIDGE · WILTS**

Taylor's REG^D N° 501079

# ZINC OXIDE PLASTER (B·P·C)




*the surgical plaster . . .*

PRESCRIBABLE ON E.C.10

EDWARD TAYLOR LTD · MONTON · ECCLES · MANCHESTER

TF234

BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 8 1961

# TREATMENT OF SCHIZOPHRENIA IN GENERAL HOSPITALS

BY

PETER ROHDE,* M.B. AND WILLIAM SARGANT, F.R.C.P.

*From the Department of Psychological Medicine, St. Thomas's Hospital, London*

The new Mental Health Act permits even the most severely ill mental patients to be treated under general-hospital conditions, and in doing so gives legal sanction to what has already been tried out experimentally for many years. In 1950 the old private-bed accommodation of the Royal Waterloo Hospital (which became part of St. Thomas's Hospital at the start of the N.H.S.) was converted into an in-patient psychiatric unit of 12 beds, and later of 20 beds, mostly in the form of single and double rooms. It was intended to provide a treatment, teaching, and research unit within the framework of a general hospital for many patients who normally would have needed admission to mental hospitals.

The unit was equipped to provide all the newer physical treatments in psychiatry, including insulin coma, E.C.T., and leucotomy. But at the same time the atmosphere was designed to resemble a general ward so far as was possible. Thus the door of the ward always remains open, patients mix with other patients from the medical and surgical wards in the occupational therapy department, and the ward is staffed by the same student nurses as the rest of St. Thomas's Hospital, but is supervised by a sister with mental nursing experience. Patients of both sexes and with all types of mental illness are admitted ; all share the same day-room and dining-room, mixing is encouraged, and the nurses are trained to foster a friendly and informal atmosphere.

## Present Series

In all, 95 patients suffering from schizophrenia have been treated in this unit from 1950 to 1959 inclusive (readmissions have not been counted—only new admissions). They were admitted from many sources. The majority came from the out-patient department of St. Thomas's Hospital, but others were referred from many parts of England for investigation and treatment. The median age of all patients was 32 years. The median length of history was two years and two months from the first onset of symptoms suggestive of schizophrenia. This figure includes 36 (38%) patients who had had previous symptoms sufficient to require medical advice or time off work. If only the median length of the attack for which they were first admitted to our unit is considered the figure is 11 months.

Most of the patients were seen and personally diagnosed as cases of schizophrenia by one of us (W.S.), and they were also discussed at weekly case conferences or teaching rounds. Only patients needing special investigation or thought likely to benefit from intensive treatment were selected for admission ; chronic deteriorated patients were excluded, and, furthermore, since the ward is an entirely open one, in earlier years the most severely disturbed cases could not be taken in, and all still have to come in voluntarily for treatment. The criteria for admission have not changed very much in the past 10 years, with the exception that since the introduction of chlorpromazine it has been possible to admit and treat more recently ill and acutely disturbed schizophrenic patients. In earlier years it was found, unfortunately, that too many of these, if admitted, had to be sent on to mental hospitals sooner or later because they could not be kept in such general-hospital surroundings without risk to themselves or others. Now this is rarely necessary, as is shown below.

*Working on a grant from the Endowment Funds of St. Thomas's Hospital, London.

## Follow-up

All the 95 patients treated in the past 10 years have now been followed up to see how they fared. They have been rated according to both their social and their psychiatric status. The social status is divided into three ratings (after Ackner *et al.*, 1957): (1) *independent*, if the patient was or is able to work and to support himself, or in the case of a housewife to run her house ; (2) *dependent*, if out of hospital, but unable to support herself or run a home ; and (3) *institutional*, if in hospital or nursing-home. The psychiatric status is rated as follows: (*a*) symptom-free, and apparently recovered ; (*b*) residual symptoms, no evidence of active schizophrenia, but some deterioration compared with premorbid personality—namely, flattening of affect, depression, or deterioration in work efficiency ; and (*c*) psychotic, evidence of active schizophrenia.

It was found that 42 patients (44%) were still regular out-patients at St. Thomas's Hospital and were seen personally by one of us (P.R.) A further 26 were also seen personally, either by making a home visit or by special appointment in the out-patient department. Six patients in hospital at the time of the follow-up were not seen, but reports were obtained from the medical superintendents. In only 13 other cases were patients not seen personally, and a rating had to be made after conversation, or a letter in a few instances, with the general practitioner or close relative. Four patients were found to be dead—two as a result of suicide. Only four patients in the series could not be reached in one way or another ; but three of these were known to be out of hospital a year and a half before, and two of them were reported to be still actively paranoid at that

time ; the fourth was also last heard of out of hospital, and probably returned to Australia. All four were rated in this inquiry as still psychotic.

The results of the whole group are shown in Table I. It was surprising to find that no fewer than 82 (86%) of the original 95 patients were out of hospital ; this is,

TABLE I.—*Results in the 95 Cases*

| | | Discharge State | Present State |
|---|---|---|---|
| Social | Independent | 16 (17%) | 66 (70%) |
| | Dependent | 62 (65%) | 16 (17%) |
| | Institutional | 17 (18%) | 9 (9%) |
| Psychiatric | Symptom-free | 12 (13%) | 46 (48·5%) |
| | Residual symptoms | 40 (42%) | 25 (26·5%) |
| | Psychotic | 43 (45%) | 20 (21%) |
| Suicide | | — | 2 (4%) |
| Unrelated death | | — | 2 |

in fact, 90% of the 91 patients still living. Even if, as is most unlikely, all four patients untraced are in fact in hospital, these figures are still 82% and 86% respectively.

It was equally surprising to find that no fewer than 71 (75%) seemed to be free from evidence of active schizophrenia, although 25 (26%) of these show evidence of residual symptoms. Throughout the 10 years, 39 (41%) of the patients have, however, had relapses which required further periods of in-patient treatment, and 31 (33%) of these relapsed within two years of leaving hospital ; a further 17 (18%) also had milder relapses not requiring in-patient treatment. However, as can be seen from Table I, most of these patients regained their former status and became stabilized again with further treatment.

### Methods of Treatment Used

Conflicting viewpoints still exist about the proper treatment of the more acute and recoverable schizophrenic illnesses. For many years one of us (Sargant and Slater, 1954) had always stressed the importance of giving insulin-coma treatment, with or without E.C.T., at the earliest possible moment ; but even with the careful selection of patients admitted, it was found not uncommonly that the patient's condition deteriorated too rapidly for this to be used under general-hospital conditions, or it proved ineffective. In fact, before 1956, no fewer than 12 of our 39 patients had to be transferred sooner or later to mental hospitals, and three required the urgent calling-in of the duly authorized officer because they were no longer controllable in an open ward.

By 1956, however, chlorpromazine had been introduced and we had started to use it in larger and more effective doses, generally combined with E.C.T. As a result insulin coma seemed to be much more rarely indicated, but some patients who were below their best weight continued to receive modified forms of insulin treatment (Sargant and Craske, 1941) until their weight was restored to normal or above it ; and sometimes the dose might be increased until light sopor or drowsiness, but not coma, occurred before interruption. These large doses of chlorpromazine combined with E.C.T. and modified insulin were continued until remission of symptoms had been obtained, and, on discharge, endeavours were also made to keep the patients for as long as possible on suitable maintenance doses of chlorpromazine or some other phenothiazine. And, more recently, the antidepressant drugs such as phenelzine (" nardil ") or imipramine (" tofranil ") have sometimes been added to the chlorpromazine during treatment, or in the follow-up period when depressive components to the total illness were present.

It is convenient to divide the patients into two main groups—those admitted before and those admitted after January 1, 1956. Before that date only four of our patients had been treated with chlorpromazine, and only one had been given as much as 300 mg. a day—a dose now thought to be the minimum for the treatment of acute schizophrenic patients. Since that date, chlorpromazine and E.C.T. have also largely replaced insulin coma. Table II shows the different treatments given to these two groups of cases.

It will be seen from Table III that in the earlier group no fewer than 12 (31%) of 39 patients had to be transferred to mental hospitals, either because they remained unimproved after treatment or because it had become too difficult to control them in an open general-hospital ward ; three of these, as already mentioned, had to be quickly removed to observation wards under the supervision of the duly authorized officer. However, it has since been found that with the use of large doses of chlorpromazine, combined with E.C.T. given as soon

TABLE II.—*Treatments Given*

| | 1950–5 | 1956–9 |
|---|---|---|
| Number of cases | 39 | 56 |
| More than 2 E.C.T.s | 18 (46%) | 31 (55%) |
| Insulin coma | 22 (56%) | 5 (9%) |
| Modified and sopor insulin | 11 (28%) | 31 (55%) |
| Chlorpromazine: Total | 4 (10%) | 47 (84%) |
| Chlorpromazine: More than 300 mg. a day | 1 | 35 (63%) |

TABLE III.—*State of Patients on Discharge*

| | | 1950–5 | 1956–9 |
|---|---|---|---|
| Total | | 39 | 56 |
| Social status | Independent | 7 (18%) | 9 (16%) |
| | Dependent | 20 (51%) | 42 (75%) |
| | Institution | 12 (31%) | 5 (9%)* |
| Psychiatric state | Symptom-free | 4 (10%) | 8 (14%) |
| | Residual symptoms | 8 (21%) | 32 (57%) |
| | Psychotic | 27 (69%) | 16 (29%)† |

* Significant, $P<0.02$. † Significant, $P<0.01$.

as possible after admission, all but the most violent and negativistic patients can now be rapidly brought under control and treated in general-hospital surroundings. This has resulted in only 5 (9%) of the group of 56 patients treated since 1956 having to be transferred to mental hospitals, and only one requiring the urgent assistance of the duly authorized officer.

Also, one cannot help being impressed by a comparison of the psychiatric states of the two groups as recorded on their discharge from the unit. No fewer than 27 (69%) of the earlier group of 39 patients still had evidence of active schizophrenia when they left hospital, whereas in the later group of 56 patients only 16 (29%) were still judged to be actively schizophrenic on discharge. The great increase in the number of patients leaving hospital with the rating " residual symptoms " in the second group was probably due to the fact that many patients whose psychosis had been quickly controlled by treatment and maintenance chlorpromazine still showed some flattening of their affect, or fatigue and residual mild depression, probably in part due to the use of maintenance chlorpromazine.

When the length of in-patient stay is considered, again a very marked advantage is shown in favour of the 1956–9 group. It was found that the average stay had

been reduced from 10.7 weeks to only 6.3 weeks. Furthermore, in the earlier group only 10 (26%) out of 39 had left hospital in less than one month, and all these 10 were still psychotic when they left, three requiring the duly authorized officer and a further four having to be transferred to mental hospitals. However, when comparison is made with the 22 patients in the 1956–9 group, whose stay was also less than a month, it is found that only 10 (45%) patients left hospital still classed as psychotic, and only four instead of seven required admission to a mental hospital. Only one patient in this later group required the calling-in of the duly authorized officer.

These figures tend to confirm the clinical impression that the later group have shown a marked improvement in overall treatment results. Table IV shows the results of a follow-up study designed to determine the actual state of these two groups of patients two years after discharge from hospital, since it is only by this method that the different lengths of follow-up can be equated. Patients leaving hospital after August, 1958, have been left out, as at the time of follow-up they had not completed two years. Two groups of 39 patients are left. The results show significant differences between the two groups, in that 20 (51%) in the first group remain psychotic after two years compared with only 8 (20%) in the later group (treated mostly with E.C.T., chlorpromazine, and modified insulin). Similarly, in the former group 12 (31%) were in hospital at the time of follow-up compared with only 2 (5%) in the later group.

TABLE IV.—*State of Patients Two Years After Discharge*

| | 1950–5 | 1956–August, 1958 |
|---|---|---|
| Total | 39 | 39 |
| Dead (unrelated) | 2 | 0 |
| Independent | 18 (46%) | 24 (61%) |
| Dependent | 7 (18%) | 13 (34%) |
| Institution | 12 (31%) | 2 (5%)* |
| Symptom-free | 14 (36%) | 12 (31%) |
| Residual symptoms | 3 (8%) | 19 (49%) |
| Psychotic | 20 (51%) | 8 (20%) |

* Significant $P<0.01$.

Some of the credit for maintaining the advantage of the later group should be given to the maintenance doses of chlorpromazine that most of these patients have continued to receive after leaving hospital. It is difficult to produce figures to confirm the clinical impression that maintenance chlorpromazine prevents relapse, since maintenance therapy was given to all those thought likely to relapse; however, in five cases it was felt that the return of schizophrenic symptoms requiring readmission to hospital was directly due to the patient leaving off chlorpromazine, and the response to further treatment helped to confirm this impression.

## Discussion

One of us (Sargant, 1958) has already put forward preliminary evidence that, in our own general-hospital unit, chlorpromazine, together with E.C.T. and modified insulin, seemed to be proving a quicker and more satisfactory method of treating early schizophrenia than the use of insulin coma, with or without E.C.T. These reported follow-up findings have helped to confirm this. It has now been found possible to treat in a general hospital many patients who would previously have required admission to a mental hospital, and also, since using large doses of chlorpromazine, we have been able to treat more patients more quickly and with better results.

We have found, however, that if acute schizophrenic cases are to be treated in an open ward in a general hospital it is essential that treatment should be started as soon as possible. Generally speaking, provided that the patient presents no real diagnostic problem, chlorpromazine should straightway be given in doses of about 300 mg. a day. This dosage should be progressively increased to a maximum of 1,400 mg. a day if necessary, and then lowered to the minimum required to control abnormal thought and behaviour. As soon as possible, and often straightway on admission, E.C.T. is also started and given at the rate of two or three treatments weekly, later being reduced to one or two treatments a week. The amount of E.C.T. given is always adjusted to each patient according to the symptoms present and the therapeutic response obtained, the position being reassessed before each treatment. In addition, modified insulin is generally used in patients who are under-weight, and, although we have no statistical evidence of its value in this series, it remains a strong clinical impression that patients are often greatly helped, and their recovery is stabilized, by restoring body weight to normal after discharge.

We have still, on occasion, tried insulin coma when other treatments have proved unsuccessful, and feel that although its use is rarely necessary—owing to the apparent efficacy of the combined method now being used—no treatment should yet be given up entirely that may help even very few patients from drifting into 30 years of chronicity in a mental hospital. And in some patients insulin coma may even yet be shown to provide a better quality of treatment remission than is seen with other methods.

It has also been surprising to find on follow-up that such good overall results have been obtained under general-hospital conditions in a disease which has generally been regarded as of such poor long-term prognosis for so many patients. However, as mentioned above, the patients admitted have been a selected group. The results we have obtained may also in part be due not only to the active physical treatment programme used, but also to the atmosphere of hope engendered in the patient who undergoes his treatment in a general-hospital *milieu*, to the more favourable amount of medical and nursing care possible in a small unit, and, finally, to the fact that early discharge with close out-patient supervision enables the treated schizophrenic to be rehabilitated as quickly as possible. No specialized forms of psychotherapy were, however, used or found necessary to obtain these results.

It has been an outstanding finding, recently seen also in other parts of the country (W. Maclay, 1960, personal communication), that such smaller active treatment units in general hospitals result in less chronicity than when similar early-recoverable psychiatric patients are sent for treatment in the larger and segregated mental hospitals. If these findings are confirmed and their treatment implications fully understood, more beds may well seem to be desirable in general hospitals for the treatment of suitable psychiatric patients.

## Summary

The results of a follow-up of 95 schizophrenic patients treated in a general-hospital psychiatric unit in the past 10 years are reported. It was found that no fewer than 82 (86%) of the original 95 patients were out of hospital, and 71 (75%) appeared free from evidence of active schizophrenia.

A comparison of two groups of patients—one treated predominantly with insulin coma and E.C.T., and the other with chlorpromazine, modified insulin, and E.C.T. —shows a significant advantage for the latter group, and a reduction of the average stay from 10.7 to 6.3 weeks. A comparative follow-up also confirms the superiority of the results of treatment in the latter group.

The methods used and the advantages of treating selected schizophrenic patients in a general-hospital setting are also discussed.

*Statistical Note.*—The probabilities were calculated by chi-square to give some estimate of the differences, but as the original selection was not randomized the tests may not be fully appropriate. We are grateful to Dr. E. D. West for statistical advice on our figures.

REFERENCES

Ackner, B., Harris, A., and Oldham, A. J. (1957). *Lancet*, **1**, 607.
Sargant, W. (1958). Ibid., **2**, 1370.
—— and Craske, N. (1941). Ibid., **2**, 212.
—— and Slater, E. (1954). *An Introduction to Physical Methods of Treatment in Psychiatry*, 3rd ed. Livingstone, Edinburgh.

# ANTICOAGULANT TREATMENT IN PROGRESSING STROKE*

BY

**A. BARHAM CARTER, M.D., F.R.C.P., D.P.M.**

*Consulting Physician, Ashford Hospital, Middlesex, Adviser in Neurology to the War Office*

It is probably agreed by most workers in the field of cerebral vascular disease that anticoagulants should not be used as a routine in the treatment of cerebral infarction, and that in the acute full-blown stroke they are contraindicated, as they are ineffective and may be dangerous. Moreover, in this type of lesion differentiation from intracerebral haemorrhage is particularly difficult and sometimes impossible. My initial experience suggested that if these acute strokes were excluded from the overall results, then treatment seemed beneficial, and so I decided to plan a controlled clinical trial of anticoagulants in patients suffering from the slower-onset type of cerebral infarction—the progressing stroke.

## Selection of Patients

The patients for this trial were selected from consecutive "stroke" admissions to the Ashford Hospital, Middlesex, during the four years 1956 to 1959. The details of these are shown in Table I.

The selection of patients was made in two ways. The first was a positive selection which included patients with a pre-hospital history of progressing symptoms and patients who after admission to hospital showed increase in severity or in distribution of their disability. The second was a negative selection made by excluding from this first selected group patients in whom past experience had shown that anticoagulants might be dangerous. I had previously found that major haemorrhage was much more likely to occur during the treatment of patients with established cerebrovascular disease if they showed any of the following features: (1) loss of consciousness at the time of commencing treatment; (2) severe hypertension, with a diastolic pressure reaching 120 mm. Hg. or above; (3) age over 70 years, with few exceptions; (4) evidence of past severe hypertension, such as cardiac enlargement, retinal changes with haemorrhages or oedema, and evidence of severe renal dysfunction; (5) xanthochromic or blood-stained cerebrospinal fluid; (6) evidence of hepatic disease or definite history of peptic ulceration, etc.

*Table I.—Analysis of Patients Admitted to Ashford Hospital Suffering from Acute Cerebral Vascular Lesions, Showing Sex and Aetiology*

| Year | No. of Patients | Male | Female | Embolism | "Thrombosis" | Haemorrhage |
|---|---|---|---|---|---|---|
| 1956 | 140 | 67 | 73 | 9 | 63 | 68 |
| 1957 | 147 | 70 | 77 | 10 | 66 | 71 |
| 1958 | 147 | 72 | 75 | 8 | 72 | 67 |
| 1959 | 136 | 73 | 63 | 7 | 76 | 53 |
| Total | 570 | 282 | 288 | 34 | 277 | 259 |

## Analysis of Material

In the four years, 122 patients out of the 277 admitted with the diagnosis of cerebral thrombosis came into the category of progressing stroke. The above-mentioned contraindications to anticoagulant therapy reduced this number to 80, and this group of 80 patients formed the series for the trial. Patients were placed in the control or treated group by random selection, and, apart from anticoagulants, were treated in the same way. Of these 80, four had to be withdrawn from the trial owing to recognized mistakes of diagnosis—two, by chance, in each group. Three had cerebral gliomata, and one, who was fortunately in the control group, had an intracerebral haematoma. In the final trial, therefore, were 76 patients, and these have been analysed according to age and sex in Table II. The distribution is seen to be reasonably even between the groups; over half the patients are between 60 and 70, and the ratio of men to women is four to three.

*Table II.—Analysis of Series According to Age and Sex*

| Age | No. of Patients | Treated | | Untreated | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| 40–49 | 8 | 2 | 2 | 3 | 1 |
| 50–59 | 26 | 7 | 5 | 8 | 6 |
| 60–69 | 42 | 12 | 10 | 12 | 8 |
| Total | 76 | 21 | 17 | 23 | 15 |

## Distribution of Infarction

The distribution of cerebral infarction was commonly in the middle cerebral territory, and of the 76 patients 65 were in this group. Of the others, 8 were in the vertebral-basilar territory with brain-stem lesions, two showed occlusion of the posterior cerebral and one occlusion of the anterior cerebral artery. This proportion of six middle cerebral infarctions to one elsewhere is close to the seven to one for all types of infarction (Murphy, 1954; Glynn, 1956; Carter, 1960) but greater than the series of Adams (1958), who in a series of 58 patients over a five-year period found middle cerebral, 22; vertebral basilar, 22; posterior cerebral, 4; lateral medullary syndrome, 3; and uncertain, 7. This surely must have been a very selective group.

*An address given on January 5, 1961, at the Third International Conference on Cerebrovascular Disease at Princeton, New Jersey, U.S.A.

### Method of Treatment

As soon as anticoagulant treatment was indicated the patients in the treated group received 125 mg. of heparin intravenously and 200 mg. of phenindione by mouth. Two further similar doses of heparin were given intramuscularly at six-hour intervals, and during the second 24 hours 150 mg. of phenindione in divided doses, and thereafter sufficient to keep the prothrombin time between two and three times the normal, for three weeks. In the fourth week the dose was slowly reduced to prevent rebound thrombotic episodes. One patient showed sensitivity, with diarrhoea and generalized erythematous rash, and the phenindione was replaced by ethylbiscoumacetate. I now use phenindione as my oral anticoagulant because I found dicoumarol was more difficult to control and I had some unfortunate experiences with regard to major haemorrhage. I therefore abandoned it in 1954 and have not used it since.

### Results

#### Assessment

The patients were followed up for six months and then an assessment was made by clinical examination, dividing them into four groups: recovered, improved, not improved, and died.

*Recovered.*—This meant that the patient noticed slight or no disability and was able to resume normal life without help and to return to full work. Some loss of fine-movement dexterity in the hand was regarded as compatible with full "recovery" if the above criteria were fulfilled. Probably all patients with initial complete hemiplegia continue to show slight pyramidal signs permanently.

*Improved.*—This meant some useful movement was possible at the elbow and wrist and that the patient required only slight assistance to get about and live a useful life. Some work was possible and walking with a stick was reasonably well tolerated.

*Not Improved.*—This implied no return of arm movement below the shoulder and a poor recovery in the leg so that considerable assistance was needed for the patient to get about. Return to work was not possible, and this group included the bedridden patient.

#### Analysis

In the control group half the patients had recovered or were substantially improved at the end of six months. Table III shows that prognosis worsens with age. In the group 40–49 years 3 out of 4 showed a good result, in the group 50–59 years 8 out of 14, and in the group 60 to 69 years 8 out of 20, although the groups are not numerically comparable. Treatment improved the recovery figures from 50 to 70% (Table IV), but this may well have arisen by chance, the odds being only ten to one against ($P=0.1$). However, this was encouraging enough to make me look at these patients a little more carefully. I first thought that the time of evolution of the stroke might be the key factor, and that those taking longer to develop might respond better to treatment. This, however, was not so. I finally found that if I separated the patients into those whose neurological deficit, although of slow onset, was clinically complete when treatment was begun, and those whose deficit was incomplete but progressing, then, although there was no prognostic difference in the controls, there was statistically significant improvement with treatment in the latter group ($P<0.05$). This, then, showed that anticoagulants seem to improve the prognosis if given before infarction becomes clinically complete (Tables V, VI, VII).

TABLE III.—*Results in Untreated Series*

| Age | No. of Patients | Recovered | Improved | Not Improved | Died |
|---|---|---|---|---|---|
| 40–49 | 4 | 2 | 1 | 1 | 0 |
| 50–59 | 14 | 5 | 3 | 4 | 2 |
| 60–69 | 20 | 4 | 4 | 7 | 5 |
| Total | 38 | 11 (29%) | 8 (21%) | 12 (32%) | 7 (18%) |

TABLE IV.—*Results in Treated Series*

| Age | No. of Patients | Recovered | Improved | Not Improved | Died |
|---|---|---|---|---|---|
| 40–49 | 4 | 2 | 2 | 0 | 0 |
| 50–59 | 12 | 5 | 4 | 2 | 1 |
| 60–69 | 22 | 6 | 7 | 7 | 2 |
| Total | 38 | 13 (34%) | 13 (34%) | 9 (24%) | 3 (8%) |

TABLE V.—*Results in Untreated Incomplete Lesions*

| Age | No. of Patients | Recovered | Improved | Not Improved | Died |
|---|---|---|---|---|---|
| 40–49 | 2 | 1 | 1 | 0 | 0 |
| 50–59 | 7 | 2 | 2 | 2 | 1 |
| 60–69 | 11 | 2 | 2 | 4 | 3 |
| Total | 20 | 5 (25%) | 5 (25%) | 6 (30%) | 4 (20%) |

TABLE VI.—*Results in Treated Incomplete Lesions*

| Age | No. of Patients | Recovered | Improved | Not Improved | Died |
|---|---|---|---|---|---|
| 40–49 | 2 | 2 | 0 | 0 | 0 |
| 50–59 | 7 | 2 | 4 | 1 | 0 |
| 60–69 | 13 | 4 | 5 | 3 | 1 |
| Total | 22 | 8 (36%) | 9 (41%) | 4 (18%) | 1 (5%) |

TABLE VII.—*Composite Results*

| Year | No. of Patients | Treated | | | | Untreated | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Lesion Incomplete | | Lesion Complete | | Lesion Incomplete | | Lesion Complete | |
| | | Group A | Group B | Group A | Group B | Group A | Group B | Group A | Group B |
| 1956 | 22 | 5 | 2 | 3 | 1 | 4 | 3 | 1 | 3 |
| 1957 | 18 | 5 | 1 | 2 | 1 | 2 | 2 | 2 | 3 |
| 1958 | 20 | 4 | 1 | 3 | 2 | 2 | 4 | 3 | 1 |
| 1959 | 16 | 3 | 1 | 1 | 3 | 2 | 1 | 3 | 2 |
| Total | 76 | 17 | 5 | 9 | 7 | 10 | 10 | 9 | 9 |
| % | 100 | 22 | 7 | 12 | 9 | 13 | 13 | 12 | 12 |

Group A = Recovered or improved. Group B = Unimproved or died.

### Pathological Material

There were seven deaths in the untreated series, five occurring in the age-group 60–69, and three deaths in the treated series with two occurring in the patients over 60. Eight necropsies were obtained out of these 10 deaths, as two of the untreated patients died at home. These deaths were sudden, occurred in bedridden patients, and, on the clinical evidence, might well have been due to pulmonary infarction. Of the five untreated patients pulmonary infarction was the cause of death in three, diffuse bronchopneumonia in one, and complete basilar occlusion in one. One of the three patients dying of pulmonary infarction had a complete carotid occlusion and the other two had mid-cerebral thrombi. Of the three treated patients coming to necropsy one had a massive infarction of the brain with no obvious thrombus but with gross atheroma of the cerebral vessels, one had a small occluding thrombus in the mid-cerebral artery with a rather haemorrhagic infarction beyond, and the third showed carotid stenosis and an unsuspected carcinoma of the bronchus.

These findings, although few in number, confirm my previous experiences (Carter, 1960) that anticoagulants may reduce the death rate in patients suffering from cerebral infarction by protecting them from pulmonary infarction, and this protection in patients over the age of 50 is in agreement with recent experience in traumatic surgery (Sevitt and Gallagher, 1959).

## Discussion

It appears from these results that anticoagulants have improved the natural history of progressing cerebral infarction in selected patients and have done no obvious harm in this particular series. In spite of this I still feel a sense of uneasiness when using anticoagulants for patients with established cerebrovascular disease. This feeling seems to stem from three uncertainties which I cannot ignore. The first is an uncertainty of whether my diagnosis is always correct, the second is an uncertainty of whether I am increasing the risk of cerebral haemorrhage by my treatment, and the third is the uncertainty of my knowledge regarding the mechanism by which anticoagulants can improve the effects of cerebral infarction. These three problems are worthy of some discussion.

The problem of diagnosis is in my opinion more difficult than has been commonly supposed, and I doubt very much if we possess a truly reliable and harmless method of differentiating cerebral infarction from small intracerebral haemorrhages. I have seen patients with proved intracerebral haematoma whose cerebrospinal fluid has contained fewer than 5 red blood-cells per ml.

The risk of cerebral haemorrhage must, I think, be increased by anticoagulant therapy, and the question is: Does this danger outweigh the advantages? My own experience has so far been fortunate, and is in accordance with that of Irving Wright and McDevitt (1954), Miller Fisher (1958), and Wells (1959). Other workers, notably de Morsier and Tissot (1957) and Vastola and Frugh (1959), have reported disturbing series; in one of these four fatal cerebral haemorrhages occurred in 55 treated patients. Perhaps the careful selection of patients as I have suggested may reduce this risk, and, indeed, I am now tending to narrow this selection even further than in this series and to exclude, for example, patients whose diastolic pressure is above 100 mm. Hg.

The third problem is the mechanism of treatment. I presume that benefit must arise in one of three ways. First, spread or propagation of the thrombus if present may be restricted either distally or centrally; and since this spread often involves anastomotic vessels anticoagulants may thus keep the infarcted area from enlarging. Secondly, they may prevent the formation of a thrombus if the infarction is caused by atheromatous narrowing without thrombosis. Thirdly, they may prevent the distal embolism of small thrombi or platelet clumps.

My own feeling is that anticoagulants do most good when large vessels are occluded or stenosed—such as the carotid, vertebral, basilar, subclavian, etc. This belief has up to now no true scientific basis, although my results in the treatment of carotid and vertebral stenosis have been better than those in the treatment of known intracerebral occlusions. The numbers have been insufficient to draw definite conclusions, and therefore this remains a clinical impression. If this is true, then the important mechanism of treatment is likely to be the prevention of embolization of microscopic or macroscopic particles arising at the point of stenosis or occlusion, and the stepwise rather than smooth course of untreated progressing cerebral infarction gives a clinical blessing to this pathological concept.

Another good reason for believing this to be the main method of benefit is that anticoagulants do not appear to prevent thrombosis recurring. We have all had the mortifying experience of seeing a major thrombosis occur while the patient was adequately controlled with a so-called effective prothrombin time. I have also noticed that when a patient has been stabilized on a maintenance dose of phenindione he may occasionally begin to need much more for no apparent reason in order to keep his prothrombin time right, and I have thought that this has more often than not preceded further thrombosis, but I have no figures to support this theory.

## Conclusion

The results of anticoagulant treatment in a selected series of patients with the clinical diagnosis of cerebral infarction suggest that the progressing type of infarction in a normotensive patient responds best to this treatment. It seems that reduction in death rate may be associated with prevention of pulmonary infarction, and in this series the treatment has not appeared to carry much risk. In spite of this, caution is needed as diagnosis is occasionally uncertain, treatment potentially dangerous, and the mechanism by which any benefit accrues is unknown.

## Summary

A series of 277 consecutive patients with the clinical diagnosis of cerebral infarction were seen at the Ashford Hospital, Middlesex, during the four years 1956 to 1959.

From these patients 80 were selected for a controlled clinical trial of short-term anticoagulant therapy. Four were withdrawn from the trial owing to errors in diagnosis.

The selection was made by including only those patients under 70 years of age with a pre-admission history or with clinical signs of a progressing disability, and by excluding those who showed loss of consciousness, severe hypertension with a diastolic pressure reaching 120 mm. Hg or more, xanthochromic or blood-stained C.S.F., or evidence of hepatic disease or past peptic ulceration.

The results after six months have been analysed and tabulated and suggest that in this series anticoagulant therapy has improved the natural history of progressing cerebral infarction, particularly when the lesion is incomplete at the beginning of treatment. Protection from pulmonary infarction by anticoagulants appears to be established, and this treatment in selected patients seems to be without serious risk.

The mode of action of heparin and phenindione in helping these patients is not yet understood, but it appears that large-vessel stenosis or occlusion responds better than small-vessel lesions, thus probably making this treatment more valuable when infarction is due to disease of extracranial arteries.

Caution is necessary in using anticoagulants for patients with cerebral infarction, as diagnosis is more difficult than is commonly supposed, the method of action of the drugs is not fully understood, and the treatment is potentially dangerous. However, it would seem that this treatment is not entirely valueless if patients are selected with care.

REFERENCES

Adams, R. D. (1958). *Cerebral Vascular Diseases*, p. 23. Transactions of the 2nd Conference of the American Heart Association, Princeton, New Jersey, 1957.
Carter, A. B. (1960). *Lancet*, **1**, 345.
Fisher, C. M. (1958). *Neurology (Minneap.)*, **8**, 311.
Glynn, A. A. (1956). *Brit. med. J.*, **1**, 1216.
de Morsier, G., and Tissot, R. (1957). Thérapeutique des Thromboses Artérielles Cérébrales. *Rapp. congrés. franç. Med.*, **1**, 130. Masson, Paris.
Murphy, J. P. (1954). *Cerebrovascular Disease*. Year Book Publishers, Chicago.
Sevitt, S., and Gallagher, N. G. (1959). *Lancet*, **2**, 981.
Vastola, E. F., and Frugh, A. (1959). *Neurology (Minneap.)*, **9**, 143.
Wells, C. E. (1959). *Arch. Neurol. Psychiat.*, **81**, 667.
Wright, I. S., and McDevitt, E. (1954). *Ann. intern. Med.*, **41**, 682.

# SURVIVAL AFTER NON-HAEMORRHAGIC CEREBROVASCULAR ACCIDENTS

## A PROSPECTIVE STUDY

BY

**JOHN MARSHALL, M.D., F.R.C.P.Ed., M.R.C.P. D.P.M.**
*Reader in Clinical Neurology*

AND

**ANTHONY C. KAESER, M.B., B.S.**
*Assistant House-physician*

*The Academic Unit, Institute of Neurology and the National Hospitals for Nervous Diseases, London*

The continued search for methods of preventing and treating cerebrovascular disease increasingly emphasizes the need for fuller knowledge of the natural history of this condition. The natural history of a chronic disease can be ascertained in two ways. A retrospective study may be carried out in which an attempt is made to ascertain the fate of a group of patients for whom previous records are available. This method has several disadvantages. Firstly, the initial records, no matter how thorough, rarely give sufficient information about the particular features it is desired to study. Secondly, difficulty may be experienced in tracing the patients. Thirdly, even when patients are traced, detailed information about events occurring between the initial illness and the time of follow-up may not be available. On the other hand, a retrospective study has the not inconsiderable advantage that it can be done quickly, time to study the original records and trace the patients being all that is required. Moreover, the deficiencies revealed may be of value when a prospective study is being designed.

The alternative method is to make a prospective study. This has the advantages that it can be specifically designed to meet the particular problems under investigation, and that steps can be taken to minimize the loss of patients from the follow-up. The main disadvantage is that the course of a chronic disease may need to be followed for months, or more commonly years, and as the patients come under observation serially the study may be very protracted.

A further problem associated with the study of the natural history of a chronic disease is the mode of presentation of the data. The method of presenting survivorship as the percentage of the total number of patients diagnosed who are known to be alive at the end of, say, five years involves certain fallacies. It takes no account of patients lost to follow-up, who are in effect treated as having died; nor does it take account of the fact that many patients will not have been under observation for the full five years. Another method of presenting the average duration of life from the time of diagnosis to the time of death is likewise fallacious, for it takes no account of the patients who are still alive and who clearly have a better prognosis. The fallacies inherent in these methods of presentation have been well described by Merrell and Shulman (1955), who have shown that "life-tables" give the most accurate picture.

In a previous communication Marshall and Shaw (1959) presented the results of a retrospective study made on a group of patients who had recovered from a cerebrovascular accident. The results were in some respects contrary to expectation. The opportunity presented by the presence of a "control" group in a long-term clinical trial of anticoagulant therapy in patients who had recovered from a cerebrovascular accident believed to be due to non-embolic cerebral infarction has therefore been utilized to make a prospective study of this condition. The results of the first three years of this study are presented here. A special feature has been that the patients have been seen by us at intervals of not longer than a month throughout the period and asked about the occurrence of minor incidents. This was of importance in view of the significance which is attached to transient ischaemic episodes in patients with cerebrovascular disease.

### Method and Material

177 patients (122 males and 55 females) have been included in the study to date, their age and sex distribution being given in Table I. These were patients who had recovered from a cerebrovascular accident which had been judged by the clinician caring for the patient at the time of its occurrence, and by ourselves subsequently, as having been due to a non-embolic cerebral infarction. As the patients were to be included in a long-term trial of anticoagulant therapy, they were selected according to strict criteria which have been outlined elsewhere (Hill, Marshall, and Shaw, 1960). The age, blood-pressure, serum cholesterol, electrocardiographic examination, site of lesion, duration of illness prior to admission to the study, and number of prior attacks were determined at the time of admission to the study. The blood-pressure recorded was the mean of six readings taken at hourly intervals, with the patient lying supine. The patients were subsequently seen at intervals of not longer than four weeks, and at each visit were questioned about the occurrence of further episodes. In the case of the nine patients who for one reason or another did not continue to attend regularly, contact was kept by means of visits from the

TABLE I.—*Age-and-Sex Distribution*

| Age in Years | Males | Females | Total |
|---|---|---|---|
| 35–39 | — | 1 | 1 |
| 40–44 | 4 | 2 | 6 |
| 45–49 | 11 | 5 | 16 |
| 50–54 | 19 | 9 | 28 |
| 55–59 | 38 | 12 | 50 |
| 60–64 | 29 | 15 | 44 |
| 65–69 | 21 | 11 | 32 |
| Total .. | 122 | 55 | 177 |

almoner or through the general practitioner. Thus reliable information was available about all the patients.

The data have been examined from two angles. Firstly, the life expectancy of the patients, and the factors influencing this, have been studied by calculating survival curves according to the method of Merrell and Shulman (1955). Secondly, the incidence of further cerebrovascular episodes, and the influence of various factors on this, have also been examined by means of the $\chi^2$ test with Yates's modification.

Because the study was to be prospective, and based upon personal and frequent observation of the patients, all calculations have been made from the time the patient came under our observation, and not from the time of the first manifestation of the disease. Events prior to the patients' coming under our observation have been studied, but only in relation to the effect they may have had on the prospective data.

As some of the patients were treated with anticoagulant therapy, the calculations have been made on 88 patients who did not receive anticoagulants plus 18 patients who were initially treated, but were withdrawn from treatment when it was decided to exclude those with high blood-pressure, giving a group of 106 patients in all. The conclusions based on this group are confirmed in the analysis of the whole group of 177 patients.

## Results

The survival curve for the untreated patients is given in Fig. 1. This shows that at one year 94% of the 72 males and 34 females were alive, and at two years 85% of the males and 89% of the females. The number of events occurring in patients observed for more than 117 weeks was not sufficient to make it worth while prolonging the curve beyond this point.

### Influence of Age

The influence of age on survival is shown in Fig. 2, which, as might be expected, reveals that patients of 60 years and over fared slightly worse, though the difference is not significant. Thus at one year the percentage of patients under 60 years (59 patients) who had survived was 96, as against 91 for the patients of 60 years and over (47 patients), and at two years the figures were 88 and 83% respectively.

Fig. 2 also provides some quantitative evidence in support of the view expressed by Carter (1959) that anticoagulant therapy may be more hazardous in older patients. If the patients of 60 years and over who received anticoagulants are included, the percentage survival at two years (76 patients) falls to 75, as against 83 for the untreated group (47 patients), whereas in the under 60 age-group percentage survival in the whole series (101 patients) is 86 as against 88 for the untreated group (59 patients).

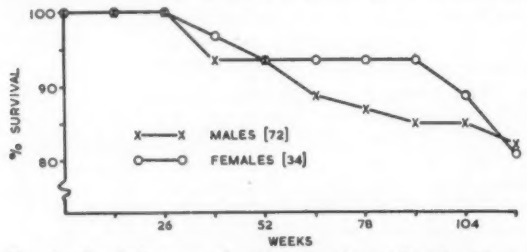



FIG. 1.—Survival curves of untreated male and female patients. In all charts the figures in brackets indicate the number of patients.

### Influence of Hypertension

The effect of high blood-pressure was most striking (Fig. 3). At one year, 64 patients whose diastolic blood-pressure as recorded by the method defined was under 110 mm. Hg at the time they came under observation showed 96% survival, whereas 42 patients with a diastolic blood-pressure of 110 mm. Hg or over showed a 90% survival. By two years, however, this gap had widened, figures of 96 and 75% being obtained, with a further drop to 66% by 117 weeks. The curves at 117 weeks differ by more than twice their standard error and are clearly significant.

### Influence of Site of Lesion

The influence of the site of lesion upon survival rate is shown in Fig. 4. As there were only six patients with stenosis of the internal carotid artery in the neck, and all survived, these have not been included. At two years 92% of the 66 patients with a focal lesion of the cerebral hemisphere had survived, as compared with 88% of the 10 patients with diffuse hemisphere lesions and 79% of the 25 patients with brain-stem lesions. Though patients with lesions of the brain stem fared worse, the numbers involved are too small to justify any firm conclusions.

### Influence of E.C.G. Findings

At the time of their entry to the study 163 patients had an electrocardiographic examination, standard leads I, II, III, aVR, aVL, and aVF, and chest unipolar leads

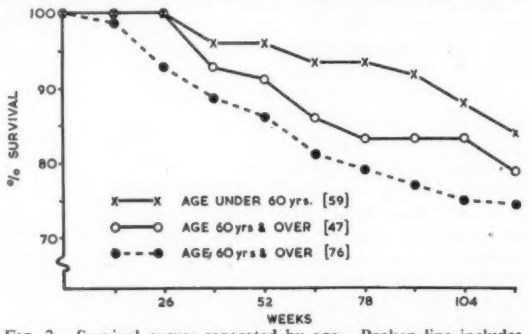



FIG. 2.—Survival curves separated by age. Broken line includes patients treated with anticoagulant therapy.

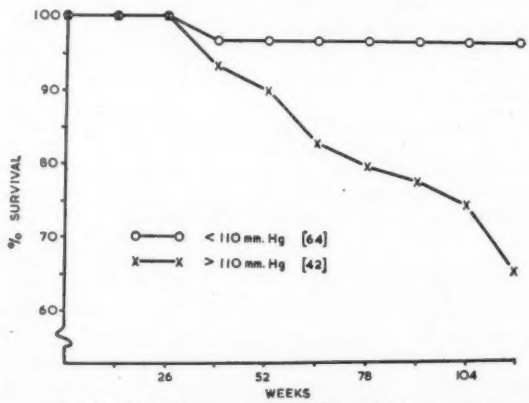



FIG. 3.—Survival curves separated by blood-pressure.

V1 to V6 being used. The records were assessed for evidence of left ventricular hypertrophy and ischaemic changes by one of us (A.C.K.). Left ventricular hypertrophy was regarded as present when there was ST depression and progressive T-wave inversion in left ventricular leads, or when the combined S wave V1 (or V2) plus the R wave V5 totalled more than 35 mm., together with normal T waves.

Apart from changes of infarction, non-specific ischaemic changes were regarded as present only when there were changes in at least two leads. Among the abnormalities were Q waves, ST depression greater than 0.5 mm., and low-voltage and abnormally shaped T waves. In three records demonstrating left bundle-branch block this was thought to be of ischaemic origin. In the two cases of atrial fibrillation there was also evidence of ischaemic changes.

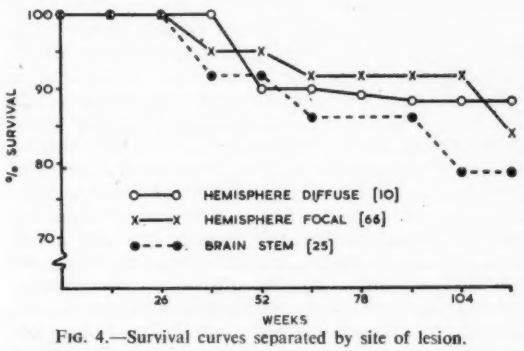



FIG. 4.—Survival curves separated by site of lesion.

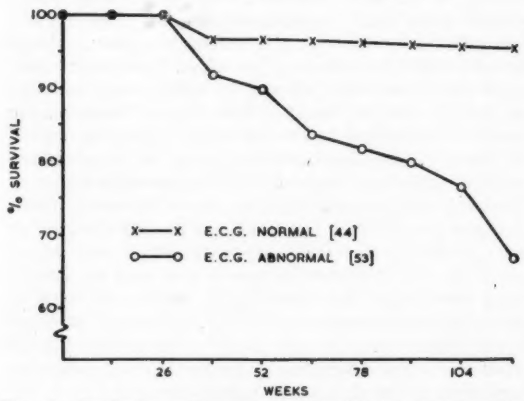



FIG. 5.—Survival curves separated according to electrocardiographic findings.

The influence of an abnormal E.C.G. upon survival in the untreated group is shown in Fig. 5, which indicates that those patients with evidence either of left ventricular hypertrophy or of ischaemic changes fared worse than those whose E.C.G. was normal. The difference between these two curves is greater than twice their standard error and is significant. This applies whether untreated patients alone are considered or those receiving anticoagulants are included.

Of the 11 patients who died from a cardiac cause, seven had an abnormal E.C.G. at the time of their admission to the study, three had a normal record, and in one the record was not done. Among the 13 patients who died from a cerebrovascular cause, 12 had an abnormal E.C.G. and one had a normal record. Five of the cardiac deaths were due to a cardiac infarction, two of the patients being among those treated with anticoagulants.

### Influence of Other Factors

Among other factors studied was serum cholesterol; the patients whose serum cholesterol level at the time they came under observation was 250 mg. or over (23 patients) were compared with those with a reading of under 250 mg. (81 patients). There was no significant difference between these two groups. The effect of the length of time which had elapsed between the first evidence of cerebrovascular disease and the time of coming under our observation was also studied. The 75 patients in whom the disease had been clinically manifest for two years or less were compared with the 31 in whom there had been symptoms for more than two years. There was no significant difference between these two. Likewise, the 84 patients who had experienced only one cerebrovascular incident before coming under observation were compared with the 22 who had experienced two or more incidents. Again there was no significant difference in their survival rate.

## Incidence of Further Non-fatal Cerebrovascular Accidents

The incidence of further non-fatal cerebrovascular accidents for the untreated patients is shown in Table II, which indicates that 11 of the 72 men and 4 of the 34 women experienced further episodes. The influence of age, blood-pressure, site of lesion, an abnormal E.C.G., and serum cholesterol on the incidence of further non-fatal cerebrovascular accidents has been calculated for both the untreated patients and the whole series, but in no instance was anything significant found. The data are given in Table II.

TABLE II.—*Incidence of Further Cerebrovascular Accidents in Untreated Cases and in Whole Series*

| | Sex | | Age | | B.P. | | E.C.G. | | Cholesterol | | Prior Attacks | | Duration of Disease Prior to Study | | Hemisphere Diffuse | Hemisphere Focal | Brain Stem | Internal Carotid |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | <60 | 60+ | <110 | 110+ | Normal | Abnormal | <250 | 250+ | 1 | 2+ | <2 Yrs. | 2 Yrs.+ | | | | |
| *Untreated Cases* | | | | | | | | | | | | | | | | | | |
| Further attacks | 11 | 4 | 10 | 5 | 9 | 6 | 5 | 14 | 13 | 2 | 8* | 7* | 9 | 6 | 3 | 8 | 3 | 1 |
| No further attacks | 61 | 30 | 49 | 42 | 55 | 36 | 39 | 39 | 68 | 21 | 76 | 15 | 66 | 25 | 7 | 58 | 22 | 4 |
| Total .. | 72 | 34 | 59 | 47 | 64 | 42 | 44 | 53 | 81 | 23 | 84 | 22 | 75 | 31 | 10 | 66 | 25 | 5 |
| *Whole Series* | | | | | | | | | | | | | | | | | | |
| Further attacks | 17 | 6 | 16 | 7 | 14 | 9 | 7 | 14 | 19 | 4 | 11† | 12† | 12‡ | 11‡ | 3 | 14 | 5 | 1 |
| No further attacks | 105 | 49 | 85 | 69 | 114 | 40 | 71 | 71 | 112 | 40 | 127 | 27 | 115 | 39 | 11 | 105 | 33 | 5 |
| Total .. | 122 | 55 | 101 | 76 | 128 | 49 | 78 | 85 | 131 | 44 | 138 | 39 | 127 | 50 | 14 | 119 | 38 | 6 |

* Significant at 1% level. † Significant at 0·1% level. ‡ Significant at 5% level.

*Influence of Number of Attacks Prior to Admission.*—The effect of this factor in the untreated group is shown in Table II, which reveals that 8 of the 84 patients who had experienced only one episode before coming under observation had a further episode during the time of observation. Of the 22 patients who had two or more attacks before coming under observation, seven had further episodes. This difference is significant ($P<0.01$). When the number of patients for analysis is increased by including those who received anticoagulant therapy (whole series) the difference becomes more significant ($P<0.001$).

*Influence of Time Prior to Admission.*—The influence of the length of time which had elapsed between the first manifestation of the disease and the time of admission to the study is given in Table II. The higher incidence of further episodes in patients whose symptoms had been present for more than two years before coming under observation was not significant in the smaller untreated group, but reached the 5% level in the larger sample provided by the whole series.

*Patients with Transient Ischaemic Episodes.*—Only 2 of the 177 patients experienced transient ischaemic episodes. Both had multiple episodes of neurological deficit, each of only brief duration. Both patients were receiving anticoagulant therapy, but neither appeared to benefit; the frequency of the attacks waxed and waned from several attacks a day to one a week or so without relation to the intensity of the therapy. The attacks continued throughout the period of observation but in neither patient led to a major episode.

### Causes of Death

Of the 177 patients 28 died. The causes of death are given in Table III, 15 being confirmed by necropsy. The table shows that vascular disease in some system was by far the commonest cause of death.

TABLE III.—*Causes of Death*

| | |
|---|---|
| Cerebrovascular | 13 |
| Coronary thrombosis | 5 |
| Other cardiac causes | 6 |
| Pulmonary embolism | 1 |
| Ruptured dissecting aortic aneurysm | 1 |
| Other causes | 2 |
| | 28 |

## Prognostic Factors

An attempt was made to see if a combination of allegedly adverse prognostic factors was present in the patients who died. A positive score was given for an abnormal electrocardiogram, serum cholesterol of 250 mg. or over, diastolic blood-pressure of 110 mm. Hg or over, more than one attack before coming under observation, and a non-fatal recurrence during the time of observation. The number of positive scores in the patients who died was not significantly higher than it was in those who had survived.

## Discussion

The life expectancy of these patients who had recovered from a cerebral infarction declined during the period of observation at a rate of about 6% a year. Comparison with other series is not very satisfactory, because of the factor of selection which inevitably arises and influences considerably the type of case included even under so specific a term as a non-embolic cerebral infarction. For example, Pincock (1957) followed 101 patients for six to eight years, but all of his patients were males. He found that 55 had died, which is a mortality rate not appreciably different from that of the present series. Similarly, Lindgren (1958) followed 65 patients with occlusion of the internal carotid for periods varying from 2 to 18 years, and found 29 deaths in all. Robinson and his colleagues (1959) prepared life-tables for 1,018 patients with a cerebral thrombosis and found a five-year mortality of 59%. All of these studies were retrospective, however.

A comparable prospective study was that of David and Heyman (1960), who followed 100 patients for two years, half of them being re-examined and half contacted by questionary. They found a 33% mortality over two years, which is much higher than that in the present study. Adams and Merrett (1961) followed 736 "hard-hit survivors" of strokes of varying causes and found that 50% of those under 65 years could be expected to survive six years and 50% of those over 65 three and a half to four years.

The value of a study of the natural history of a disease does not lie solely in the measure of overall mortality that it provides. Of more importance is information about the factors which influence prognosis, and the guidance which may be given regarding future lines of therapeutic endeavour. The most striking feature in the present study was the adverse effect of hypertension upon survival, the two-year life expectancy decreasing from 96 to 75%. This finding confirmed that of Lindgren (1958) in his series. The observation is of considerable importance, for it has been suggested (McMichael, 1952) that the occurrence of a cerebrovascular accident in a patient with hypertension contra-indicates hypotensive therapy, or at least demands great caution in its use. Smirk (1957), on the other hand, did not think that "an old hemiplegia of mild degree" contraindicated the use of hypotensive agents, though he mentioned that lowering the blood-pressure in acute cases was sometimes followed by a temporary increase in the neurological deficit. This fear of reducing the cerebral blood-flow below the critical level has tended to dominate the approach to therapy in hypertensive patients who have evidence of cerebrovascular disease. That hypotensive episodes may induce further cerebrovascular symptoms is not to be denied, but the crux of the problem is the frequency with which this occurs when modern hypotensive agents are used by people with experience. The risk would need to be high to outweigh the severe mortality associated with untreated hypertension found in this study. The present figures justify a more enterprising approach to hypotensive treatment to see if this will reduce mortality.

The second striking feature was the marked tendency for patients who had experienced several cerebrovascular accidents before coming under observation to have further accidents. This is in keeping with the findings of Pincock (1957) and of David and Heyman (1960). Indeed, so pronounced is this difference that it suggests that patients with cerebral infarction might be divided into two groups. The first comprises those patients who experience one cerebral infarction and have had no recurrence for many years. These may be termed the inactive group. The second comprises those patients who continue to have cerebrovascular episodes. These may be termed the active group.

The concept of activity and inactivity, though familiar to cardiologists in their consideration of ischaemic heart disease, has received little attention in cerebrovascular disease. Concepts such as occlusion or stenosis of

vessels, falls in blood-flow below a critical level, and the adequacy of collateral circulation have dominated thinking. Little attention has been paid to the state of the blood passing through the stenosed segments or via collateral vessels. It is worth while investigating the possibility that a disturbance of the dynamic balance which exists between the coagulation and fibrinolytic systems in the blood may provide a more satisfactory explanation for recurrent cerebrovascular episodes than do the mechanistic explanations, such as hypotensive episodes or recurrent emboli, which have been hitherto invoked.

The concept of activity and inactivity has further importance, for, if patients could be assigned to the appropriate group, therapy need only be given to those in an active state of the disease. It has been shown that anticoagulant therapy is not without hazard when given to all types of patient who have recovered from a cerebral infarct (Hill *et al.*, 1960). But there may be special groups who will benefit from anticoagulant therapy. The experience of Fisher (1958) in the treatment of patients who are having numerous minor transient episodes suggests that they constitute one such group. Patients of the type encountered in the present study who experience recurrent major episodes might constitute another group, and are worth studying from this point of view.

The influence of repeated cerebrovascular accidents on survival must also be considered. In their retrospective study, Marshall and Shaw (1959) found only 7 patients with recurrences among 102 survivors. They raised the possibility that the incidence might have been much higher among those who had died but on whom information on this point was lacking. Pincock (1957) found a higher mortality among those who had recurrent episodes, and David and Heyman (1960) observed that a history of a previous infarct increased the mortality from a subsequent infarct from 25 to 61%. In the present study there was no significant difference in the life expectancy between those patients who had experienced only one attack prior to coming under observation and those who had experienced two or more attacks. Nor did the occurrence of attacks subsequent to the patients' coming under observation appear to be closely related to prognosis for life. Though one patient had five episodes in the two years prior to death, this pattern was not found among the other patients who died.

An important prognostic factor which emerged from the study was the presence of changes indicative of left ventricular hypertrophy or of ischaemic heart disease in the electrocardiogram. Patients with these changes fared much worse so far as life expectancy was concerned, though they did not appear to be more liable to non-fatal cerebrovascular accidents. This diminished survival rate was partly due to the occurrence of coronary thrombosis in this group; but that was not the whole explanation, for there was a significantly higher incidence of abnormal E.C.G. records among those who died from a cerebrovascular cause.

The commonest cause of death was a cerebrovascular accident, but this only slightly exceeded cardiovascular causes. The fact that 26 of the 28 patients died from some form of cerebrovascular disease underlines the well-known fact that cerebrovascular disease is but one manifestation of the diffuse disease of atherosclerosis. The assessment of a patient with cerebrovascular disease cannot therefore be based on the neurological findings alone, but must take into account the presence and degree of activity of vascular disease in other systems.

The minute incidence of transient ischaemic episodes in this series is remarkable, especially in view of the great interest these episodes have aroused. The low incidence was not due to failure to diagnose such cases, for the patients were seen regularly at monthly intervals and questioned about the occurrence of any symptoms since their previous visit. The fact that only two patients experienced this type of episode makes it impossible to say anything about their significance in heralding a major stroke, or of their general prognostic value. Certainly they do not appear to be a common residuum of a cerebral infarction, nor in the present series studied prospectively did they give warning of an impending infarction.

The value of a study of the natural history of a disease is not what it records about the past but the signposts it erects for the future. This study has high-lighted two problems for further study. The first is the correct management of patients who have recovered from a cerebral infarction but who have hypertension. Will carefully controlled hypotensive therapy improve their prospects, and, if so, should it be combined in suitable cases with anticoagulant therapy or not? The second problem is whether patients with cerebrovascular disease can be divided prospectively into two groups—those in whom the disease is active and those in whom it appears to be inactive; and, if so, what is the aetiological basis of this difference, and how should the groups be treated? The continued study of the natural history of the condition over a longer period, and the reappraisal of material from these standpoints, may lead to a closer understanding of this polymorphic disease.

## Summary

177 patients who had recovered from a cerebral infarction were admitted serially to a prospective natural history study over a period of three years; the factors influencing their progress have been measured by means of life-tables.

The presence of a diastolic blood-pressure of 110 mm. Hg or over or of an abnormal E.C.G. significantly impaired life expectancy.

Patients who had experienced several cerebrovascular accidents before coming under observation had a significantly higher incidence of subsequent attacks.

The indications provided by the study for further work in cerebrovascular disease are discussed.

We thank the Nuffield Foundation for their generous support of our studies in cerebrovascular disease of which the present study forms a part.

## References

Adams, G. F., and Merrett, J. D. (1961). *Brit. med. J.*, **1**, 309.
Carter, A. B. (1959). *Quart. J. Med.*, **28**, 125.
David, N. J., and Heyman, A. (1960). *J. chron. Dis.*, **11**, 394.
Fisher, C. M. (1958). *Neurology*, **8**, 311.
Hill, A. B., Marshall, J., and Shaw, D. A. (1960). *Quart. J. Med.*, **29**, 597.
Lindgren, S. O. (1958). *Acta psychiat. scand.*, **33**, 343.
McMichael, J. (1952). *Brit. med. J.*, **1**, 933.
Marshall, J., and Shaw, D. A. (1959). Ibid., **1**, 1614.
Merrell, M., and Shulman, L. E. (1955). *J. chron. Dis.*, **1**, 12.
Pincock, J. G. (1957). *Ann. intern. Med.*, **46**, 925.
Robinson, R. W., Cohen, W. D., Higano, N., Meyer, R. Lukowsky, G. H., McLaughlin, R. B., and MacGilpin, H. H., jun. (1959). *J. Amer. med. Ass.*, **169**, 1149.
Smirk, F. H. (1957). *High Arterial Pressure*. Blackwell, Oxford.

# MANAGEMENT OF PULMONARY TUBERCULOSIS DURING PREGNANCY

BY

**RONALD B. PRIDIE,* M.B., B.S.**
*Lately Medical Registrar*

AND

**PETER STRADLING, M.D., M.R.C.P.**
*Chest Physician and Lecturer*

*From Hammersmith Chest Clinic and the Postgraduate Medical School of London*

It was long held that the first trimester of pregnancy and the immediate post-partum period were particularly dangerous times in the life of a woman with tuberculosis. Review of the literature of recent years, however, shows that there have been numerous papers which failed to support this view.

On the contrary, although statistical proof is lacking, most authors claim that pregnancy has little detrimental effect on the tuberculosis. This conclusion was common in the literature even before the chemotherapy era (Cohen, 1946 ; Friedman and Garber, 1946 ; Stewart and Simmonds, 1947).

If the mass of evidence failed to prove the harmfulness of pregnancy before the advent of chemotherapy, how much safer must pregnancy be in the tuberculous woman to-day. This is fully endorsed by many authors (Kruger *et al.*, 1951 ; Hedvall, 1953 ; Pugh, 1955 ; Rosenbach and Gangemi, 1956 ; Schaefer *et al.*, 1957 ; Lane, 1957) and by the Joint Tuberculosis Council (1958). In spite of the lack of full statistical proof, it is now reasonable to accept this conclusion.

Nevertheless, some physicians still treat the pregnant woman with quiescent disease by prolonged bed rest, either before or after delivery and sometimes during both periods ; some routinely ban breast-feeding even if the mother is non-infectious. The use of chemotherapy is by no means standardized, but termination of pregnancy is now rarely practised for tuberculosis alone. It would seem that even to-day there is not unanimity of practice in managing these patients.

In an effort to reach some logical conclusions in this matter, a retrospective study of the cases managed at Hammersmith Chest Clinic of recent years has been carried out.

## Method

The notes of all female patients on the Hammersmith Chest Clinic tuberculosis register in early 1959 were examined. Those patients who had been delivered within five years of previous activity of their tuberculosis were chosen for analysis. Each pregnancy was considered separately, giving a total of 103 pregnancies in 73 patients : some patients thus appear more than once in the analysis of results. Patients whose disease was first discovered during a pregnancy were excluded.

In making the analysis, age, extent of disease, chemotherapy, rest, and breast-feeding were all considered with the relapses in an effort to discover or exclude possible relationships.

A woman was thought to have had active disease within the preceding five years if during that period she produced a positive sputum or laryngeal swab, and/or showed change in her radiographs. Any patient with a pneumothorax was not regarded as quiescent until it had been abandoned.

Relapses were regarded as possibly related to the pregnancy, and therefore analysed, only if occurring within eight months prior to delivery or in the immediately succeeding year. Such reactivation was defined as the reappearance of either a positive sputum or laryngeal swab and/or radiological spread.

In assessing the extent of disease the grades employed were equivalent to minimal, moderately advanced, and severe of the American system (National Tuberculosis Association, 1950).

When considering the chemotherapy received by the patients, four categories were used : (1) no chemotherapy or less than three months' total chemotherapy ; (2) three months' or more chemotherapy during initial treatment only ; (3) three months' or more chemotherapy during pregnancy only ; and (4) three months' or more chemotherapy during both initial treatment and pregnancy.

Rest was defined as "confined to bed for one month or more prior to delivery." Patients were included in the category "breast-feeding" only if they had continuously suckled for at least one month.

## Results

In Table I the age distribution and extent of disease are set out in relation to the chemotherapy given. There is no significant difference between the age groupings in the various chemotherapy categories, and the various extents of the disease have similar distributions.

Table II shows that there was no real difference in the distribution of extent of disease between those patients who suffered a relapse and those who did not. The figures presented in Table III thus are significant : it will be seen that those women who received chemotherapy for the treatment of their original disease suffered a

TABLE I.—*Age and Extent of Disease*

| Chemotherapy | Extent of Disease | | | | Age in Years | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Min. | Mod. Adv! | Severe | Total | -19 | -29 | -39 | 40 + | Total |
| None | 27 | 17 | 7 | 51 | 0 | 27 | 22 | 2 | 51 |
| During initial treatment only | 15 | 3 | 6 | 24 | 3 | 11 | 10 | 0 | 24 |
| During pregnancy but none initially | 3 | 0 | 3 | 6 | 1 | 2 | 3 | 0 | 6 |
| Initially and during pregnancy | 12 | 4 | 6 | 22 | 4 | 10 | 7 | 1 | 22 |
| Total | 57 | 24 | 22 | 103 | 8 | 50 | 42 | 3 | 103 |

TABLE II.—*Relapse and Extent of Disease*

| Extent of Disease | Relapse | No Relapse | Total |
|---|---|---|---|
| Minimal | 12 | 45 | 57 |
| Moderately advanced | 5 | 19 | 24 |
| Severe | 3 | 19 | 22 |
| Total | 20 | 83 | 103 |

TABLE III.—*Relapse and Chemotherapy*

| | Chemotherapy During Pregnancy | | | No Chemotherapy During Pregnancy | | |
|---|---|---|---|---|---|---|
| | Initial Chem. | No Initial Chem. | Total | Initial Chem. | No Initial Chem. | Total |
| Relapse | 0 | 0 | 0 | 3 | 17 | 20 |
| No relapse | 22 | 6 | 28 | 21 | 34 | 55 |
| Total | 22 | 6 | 28 | 24 | 51 | 75 |

*Now at University College Hospital, London.

much lower breakdown rate (3 out of 46=7%) than those who did not (17 out of 57=30%). None of the 28 patients who received chemotherapy during pregnancy relapsed, compared with 20 out of the 75 (27%) who did not. Of those who received neither original nor pregnancy chemotherapy, 33% relapsed.

A further analysis of the relapses showed that the rate for those mothers who breast-fed was only one-fifth of that for those who did not. A valid causal association cannot be assumed here, however, because this finding is open to the criticism that only patients with apparently quiescent disease would be allowed to feed their infants.

There was no difference in relapse rate between the patients who rested and those who did not; but there were only 14 in the resting group. This number is too small to allow of valid conclusions. Other evidence that rest is unnecessary during treatment with chemotherapy is, however, quite convincing (Tyrrell, 1956; Wier *et al.*, 1957; Tuberculosis Chemotherapy Centre, 1959; Tuberculosis Society of Scotland, 1960; Wynn-Williams and Shaw, 1960).

## Discussion and Conclusions

In a retrospective survey of this kind there can be no control series and therefore no statistically valid scientific conclusions can be drawn. We can, however, state that the patients who received chemotherapy during pregnancy were reasonably comparable with those who did not, and that they suffered no relapse during pregnancy and during the subsequent year. This effect of chemotherapy is presumably independent of pregnancy.

It will be noted that the relapse rate in those patients who never received chemotherapy is high (20 of 75=27%). Since we can never know what the relapse rate would have been without pregnancies, our findings can throw no new light on the effect of pregnancy on the course of pulmonary tuberculosis.

From our results we can, however, conclude that the pregnant woman with pulmonary tuberculosis that has shown any sign of activity within the previous five years can safely undertake pregnancy and labour without relapse, *provided that she receives adequate chemotherapy at this time.* Furthermore, rest and breast-feeding have no bearing on the prognosis provided chemotherapy is given.

We feel that ambulant chemotherapy should be given on the slightest suspicion of activity either during the pregnancy or in recent years, and that this alone will protect a mother from a tuberculous recrudescence at this critical time. Provided the patient is well and the disease uncomplicated, rest should not be prescribed, and breast-feeding can be allowed by all parents who prove bacteriologically negative; apart from chemotherapy the mother can lead a normal life.

Floridly active tuberculosis is, naturally, another problem, but even in these cases it is our experience that more than a few weeks' rest is unnecessary, and that most cases can be rendered sputum-negative or laryngeal-swab-negative before delivery (and thus often safe to breast-feed) provided the diagnosis is made in reasonable time. The incidence of pulmonary tuberculosis in pregnancy is no less than in the general population. For instance, in the antenatal clinic at Hammersmith Hospital during 1958 and 1959, when 5,386 women had routine chest radiographs, a total incidence of 9.3 per thousand was discovered, about 2 per thousand proving to be previously undiagnosed active cases (Browne and Browne, 1960). Routine antenatal chest radiography, best undertaken in the fourth month of pregnancy to minimize radiation hazards, is thus not only desirable to exclude tuberculosis in the majority but vital to obtain the prompt diagnosis necessary in the few.


## Summary

The records of 103 pregnancies occurring in 73 women with pulmonary tuberculosis, active within the previous five years, were analysed in an attempt to discover any relationship between treatment with chemotherapy, rest given during the pregnancy, or breast-feeding on the one hand and subsequent relapse of the disease on the other.

No relationship could be shown between relapse and rest or between relapse and breast-feeding.

Of those patients who received chemotherapy during pregnancy, none relapsed, compared with 27% of those receiving no chemotherapy.

It is concluded that the pregnant woman with pulmonary tuberculosis showing any signs of recent activity can safely undertake pregnancy and labour without relapse provided she receives adequate chemotherapy at this time. In these circumstances rest is unnecessary and the patient can be ambulant.

Non-infectious patients thus treated can safely be allowed to breast-feed after delivery. Even patients found infectious early in pregnancy can often be rendered non-infectious in time to suckle their infants.

The continued application of routine antenatal chest radiography is essential to discover tuberculosis early enough to ensure this adequate control of the disease by the time of delivery.


We are grateful to Professor J. C. McClure Browne for his constructive criticism of this paper.

### REFERENCES


Browne, F. J., and Browne, J. C. M. (1960). *Antenatal and Postnatal Care*, 9th ed. Churchill, London.

Cohen, R. C. (1946). *Brit. J. Tuberc.*, **40**, 10.

Friedman, L. L., and Garber, J. R. (1946). *Amer. Rev. Tuberc.*, **54**, 275.

Hedvall, E. (1953). *Acta med. scand.*, **147**, Suppl. 286.

Joint Tuberculosis Council (1958). *Antenatal and Obstetric Care of Tuberculous Patients and Measures to Safeguard Their Infants.*

Kruger, A. L., Cosgrove, R. S., and Cosgrove, S. A. (1951). *Virginia med. Monthly*, **78**, 417.

Lane, R. M. (1957). *Canad. med. Ass. J.*, **77**, 28.

National Tuberculosis Association (1950). *Diagnostic Standards and Classification of Tuberculosis*, 9th ed. New York.

Pugh, D. L. (1955). *Brit. J. Tuberc.*, **49**, 206.

Rosenbach, L. M., and Gangemi, C. R. (1956). *J. Amer. med. Ass.*, **161**, 1035.

Schaefer, G., Birnbaum, S. J., and Douglas, R. G. (1957). Ibid., **165**, 2163.

Stewart, C. J., and Simmonds, F. A. H. (1947). *Brit. med. J.*, **2**, 726

Tuberculosis Chemotherapy Centre, Madras (1959). *Bull. Wld Hlth Org.*, **21**, 51.

Tuberculosis Society of Scotland (1960). *Tubercle (Lond.)*, **41**, 161.

Tyrrell, W. F. (1956). *Lancet*, **1**, 821.

Wier, J. A., Taylor, R. L., and Fraser, R. S. (1957). *Ann. intern. Med.*, **47**, 762

Wynn-Williams, N., and Shaw, J. B. (1960). *Tubercle (Lond.)*, **41**, 352.


The Research Defence Society has published No. 13, *Animal Experiments in the Control of Animal Disease*, in its Conquest Pamphlet series. It costs 6d. from the Society at 11 Chandos Street, Cavendish Square, London W.1.

# LATENT BRUCELLOSIS IN FARMERS

BY

IAN McWHINNEY, M.D., M.R.C.P.
*General Practitioner, Stratford-on-Avon*

AND

A. P. PRIOR, M.B., B.S.
*Consultant Pathologist, South Warwickshire Hospital Group*

The incidence of undulant fever in Great Britain is not known. Wilson (1932) estimated it to be between 400 and 500 new cases per annum. Dalrymple-Champneys (1960) regards this as an underestimate, and puts the figure at about 1,300 per annum. In a recent survey of brucellosis in Oxfordshire, Bothwell (1960) found three hospital admissions in one year from a population of one million. The number of cases diagnosed but not admitted was not known, but, assuming the admission rate of 33% suggested by Smith (1951), Bothwell arrived at an annual incidence of 9 cases per annum per million people. If the incidence is uniform over the country as a whole this would suggest that the annual incidence for Great Britain is about 450 cases. As Dalrymple-Champneys has pointed out, undulant fever is often a mild illness which can run its course or be terminated by antibiotics without being diagnosed. It seems likely, therefore, that the actual incidence is considerably in excess of the number of cases diagnosed.

In the United States undulant fever is now regarded as almost entirely an occupational disease of those who handle infected animals or meat. Spink (1956) concluded that not more than 10% of cases were due to consumption of unpasteurized milk. The picture in Great Britain appears to be quite different. Only 236 of the 1,500 patients studied by Dalrymple-Champneys were in exposed occupations. In the Oxfordshire survey only 22% of the adults acquired their infection by direct contact.

Epidemiological studies of people in exposed occupations have revealed that a certain proportion of them have brucella agglutinins in their serum, although they have never had an attack of undulant fever. Since, with few exceptions, the presence of brucella agglutinins is due to invasion of the tissue at some time by brucella organisms, it is concluded that these people have had a latent brucella infection (Spink, 1956). Similarly, a proportion of people in these occupations give a positive reaction with the brucellin skin test. This reaction is due to a specific hypersensitivity to the brucella antigen —a state which can be produced only by invasion of the tissues by brucella organisms (Spink, 1956). It has therefore the same significance as the presence of agglutinins in the serum.

Arblaster and Prior (1956) performed brucellin skin tests and agglutination reactions on 18 Warwickshire veterinarians. All except two of these gave positive skin reactions, some of them strongly positive and incapacitating. Only 2 of the 18 had agglutinins present before the skin test. Two weeks after the skin test four had agglutinins to a titre of 1 in 20, one to a titre of 1 in 40, and two to a titre of 1 in 320.

Taking as their criterion a brucella agglutinin titre of 1 in 80, Damon *et al.* (1950) found a latent infection rate of 3.7% in 190 male farm-workers from Indiana. So far as we know there have been no similar studies of the farming population in this country.

## Present Investigation

The subjects of this study were 20 volunteers from one general practice. Of 22 men who were approached only two declined to take part. The 20 comprised 13 self-employed farmers, three farm managers, one pupil, and three farmers' sons working on their fathers' farms. Their ages ranged from 19 to 73. No man known to have had undulant fever was included. Fifteen different farms were represented in the survey.

At the first visit a medical history was taken, a detailed inquiry being made into all febrile illnesses. Blood was taken for the first agglutination test and a brucellin skin test was performed. This was read 48 hours later and the result placed in one of four categories. (1) Very strongly positive (+++): induration of 1 cm. diameter or more; erythema of 3 cm. diameter or more; general symptoms such as malaise, headache, or/and limb pains. (2) Strongly positive (++): a reaction of the same dimensions as (1), but with no general symptoms. (3) Positive (+): induration of 0.5–1 cm.; erythema of 2 cm. (4) Negative (−): erythema only, or no reaction at all.

At the third visit, between two and four weeks after the first, the second blood sample was taken. Two men failed to attend for the second test, and in one other the second specimen was mislaid.

The agglutination tests were performed by the technique described by Spink (1956) A fixed dose of antigen mixed with appropriate serum dilutions is read at 48 hours after incubation at 37° C. This gives easily readable results and clear end-points.

## Results

The results are summarized in the accompanying Table. The brucellin test was very strongly positive in five, strongly positive in five, positive in one, and negative in nine. Antibodies to a titre of 1 in 40 or more were present at the first test in eight (three brucellin +++, two ++, and three −) and at the second test in 10. Two others had antibodies to a titre of 1 in 20 at the first test. Eight showed a rise in titre at the second test. In three of these the increase was threefold or greater (all brucellin +++); in one it was twofold (brucellin ++); and in four the titre was doubled (one +++, one ++, one +, and one −). In the one negative reactor the rise was only from nil to 1 in 20.

*Summary of Results*

| Subject | Age | Brucellin Test | 1st Agglutination Test | 2nd Agglutination Test |
|---|---|---|---|---|
| 1 | 47 | +++ | Nil | 1/640 |
| 2 | 50 | +++ | 1/320 | 1/640 |
| 3 | 27 | +++ | 1/320 | 1/320 |
| 4 | 73 | + | 1/20 | 1/40 |
| 5 | 39 | − | 1/40 | 1/40 |
| 6 | 36 | +++ | 1/40 | 1/640 |
| 7 | 42 | − | Nil | Nil |
| 8 | 39 | +++ | ,, | 1/80 |
| 9 | 35 | ++ | 1/20 | 1/20 |
| 10 | 32 | ++ | Nil | Nil |
| 11 | 19 | − | 1/40 | 1/40 |
| 12 | 60 | ++ | Nil | Nil |
| 13 | 19 | − | 1/80 | — |
| 14 | 21 | ++ | 1/40 | 1/80 |
| 15 | 38 | − | Nil | 1/20 |
| 16 | 50 | ++ | 1/40 | 1/160 |
| 17 | 29 | − | Nil | Nil |
| 18 | 24 | − | ,, | ,, |
| 19 | 32 | − | ,, | − |
| 20 | 37 | − | ,, | − |

### Evidence of Undiagnosed Undulant Fever

None of the participants showed any evidence of undulant fever at the time of investigation. From our inquiries into their past histories, however, we believe that two of them had undiagnosed attacks in the past.

*Case 6.*—This man at first denied any history of febrile illness. The symptoms produced by his brucellin test (malaise, headache, limb pains, sweating) recalled to his memory an illness with exactly similar symptoms which he had suffered 10 years previously. It lasted three months, but was not serious enough to cause more than a few days' loss of work. His doctor found no abnormality, and sent him to hospital for pathological tests. It seems that these were of little help, because no satisfactory diagnosis was made and the symptoms disappeared spontaneously.

It was not possible to obtain further clinical details or the results of the pathological tests. Nevertheless, we believe that the patient's description of his illness is fully consistent with a diagnosis in retrospect of the ambulant form of undulant fever.

*Case 12.*—Between 1936 and 1940 this farmer had experienced several bouts of fever with profuse sweating, each one lasting several days. At the time he was having much trouble with contagious abortion in his milking herd. His doctor was unable to find the cause of the pyrexia, but commented that the clinical picture resembled malaria. The patient had not, however, been abroad. About the year 1950 he had a prolonged pyrexial illness which kept him off work for three months, including convalescence. The pyrexia was swinging and accompanied by profuse sweating, malaise, and limb pains. There was no response to penicillin or sulphonamides, but the fever subsided promptly with chloramphenicol and there was no recurrence.

### Discussion

If either a positive brucellin test or brucella agglutinations to a titre of at least 1 in 40 are taken as evidence of past or present latent infection, then the latent infection rate in this series is 14 out of 20, or 70%. The area is one of mixed arable and stock farming, with no preponderance of dairy herds, and there is no reason to think that these results could not be reproduced in other parts of the country with a similar agriculture. Vaccination of cattle with strain 19 has led to a decreased incidence of abortion (Stableforth, 1960). The proportion of positive milk samples has also decreased, but not to the same extent. In the veterinary section of the Oxfordshire brucellosis survey, between 4.4 and 8% of farms were found to be producing infected milk at the time of the test (McDiarmid, 1960). In spite of recent improvements in the abortion rate in cattle, it appears from the present survey that brucella infection is still widespread among farmers. Although the majority of those who contract the infection suffer no ill-health, it is interesting to find that 2 out of 20 (10%) in this series have almost certainly had undiagnosed undulant fever. This supports Dalrymple-Champney's contention that the real incidence of the disease is higher than its reported incidence. It also emphasizes the importance of considering undulant fever whenever a farmer or farm worker presents with a pyrexia of unknown origin or with vague symptoms such as malaise, limb pains, and sweating.

From the results of the agglutination reactions shown here it is evident that a titre of up to 1 in 320 is of no diagnostic value in a farmer, nor is a rise in titre after a positive brucellin test.


### Summary

A survey of 20 farmers for latent brucellosis is described. Brucellin skin tests were performed, and serum agglutination tests both before and after the skin test.

Taking a positive brucellin test or the presence of agglutinins to a titre of 1 in 40 as the criterion of latent infection, we found a latent infection rate of 70%. As a result of inquiries into their past medical histories it is concluded that two of the farmers have almost certainly suffered from undiagnosed undulant fever.



REFERENCES

Arblaster, P. G., and Prior, A. P. (1956). *Vet. Rec.*, **68**, 969.
Bothwell, P. W. (1960). Ibid., **72**, 425.
Dalrymple-Champneys, Sir W. (1960). *Brucella Infection and Undulant Fever in Man.* Oxford Univ. Press, London.
Damon, S. R., Scruggs, J. H., and Parker, E. B. (1960). *J. Amer. vet. med. Ass.*, **117**, 39.
McDiarmid, A. (1960). *Vet. Rec.*, **72**, 423.
Smith, J. (1951). Quoted by Bothwell (1960).
Spink, W. W. (1956). *The Nature of Brucellosis.* Univ. of Minnesota Press, Minneapolis.
Stableforth, A. W. (1960). *Vet. Rec.*, **72**, 419.
Wilson, G. S. (1932). Ibid., **12**, 1240.


## INCIDENCE OF NON-CENTRAL FIXATION IN CHILDREN WITH SQUINT


BY

**JOHN SCULLY, M.B., Ch.B., D.P.H., D.O.M.S.**

*Senior Hospital Medical Officer, Manchester Royal Eye Hospital; Oculist to the Education Authority, Salford, Lancs*

AND

**E. J. NAYLOR, M.Sc.Tech., Ph.D.**

*Research Fellow in Ophthalmic Optics, Department of Ophthalmology, Manchester University*


Amblyopia, or diminution of vision in one eye, has long been recognized as a major factor to be reckoned with in the treatment of children with squint. A monocular visual deficiency or a recognizable squint is frequent in the child population of pre-school (under 5) and school (5–15) years in the urban areas in this country, and may reach a figure of 5%. Those children who have monocular convergent squint may develop amblyopia in the deviating eye. It is generally accepted that an eye may be regarded as amblyopic when the visual acuity is less than 6/12 or when the affected eye sees two or more lines fewer than its fellow on the Snellen chart, in the absence of pathological change.

Considerable interest has been taken in this subject recently, and it has been shown by Cole (1959) that 7.7% of children up to the age of 10 are amblyopic in one eye, compared with a figure of 5.27% for all age-groups in the adult population. The greater proportion of the amblyopia of childhood is due to squint, and the classical treatment—occlusion of the fixing eye (when performed up to the age of 7)—results in cure or improvement in visual acuity in those patients who persevere in the treatment. There remains, however, a number of patients in whom the amblyopia is intractable; in a recent series at the Manchester Royal Eye Hospital this intractability was found in 17% of patients under 10 with convergent strabismus (Naylor and Wright, 1959). A large proportion of these amblyopes

have fixation in the squinting eye which is not centred on the fovea. The incidence of such non-central fixation in amblyopia has been given by Von Noorden (1960) as 44% and Cüppers (1958) as 35.5%. The incidence of non-central fixation in squint in this country is not known and may well be different from that on the Continent, since the school medical and maternity and child welfare services here have been active over many years in the ascertainment of squint. Reference to the school ophthalmic clinics and to eye hospitals, where correction of refraction and orthoptic supervision is available, is (or should be) a routine matter.

In order to elucidate the incidence of non-central fixation in children in this country, routine examination of the fixation in patients attending for the first time with a squint at an eye hospital (Manchester Royal Eye Hospital) and at a school ophthalmic clinic (Salford Education Department) has been carried out, together with a similar routine examination of patients attending the school clinic who have already had treatment for their squint. The primary purpose of the present paper is to assess the frequency of non-central fixation in the new patients attending the hospital, and to study the factors which influence this frequency.

## Method

Young patients with squint who attended the Manchester Royal Eye Hospital for the first time were examined under mydriasis to determine the refractive error and the type of fixation. The latter was determined by using the "visuscope," which is an instrument similar to the ophthalmoscope whereby a small black star is projected on to the retina and the child is asked to look at it, the other eye being covered temporarily. The observer can see the image of the star resting on the fundus; if central fixation is present, the star remains steadily on the foveola, but if non-central fixation is present the star is seen in one of the following five different areas (see Fig. 1):

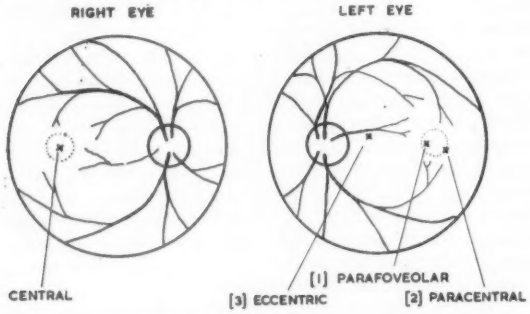



FIG. 1.—Diagrammatic representation of fundi seen with visuscope. Right eye: central fixation. Left eye: (1) parafoveolar, (2) paracentral, (3) eccentric, fixation.

A. *Unsteady Central Fixation:* In this case the star hovers over the foveola and the perifoveolar area but is not steadily fixated on the foveola.

B. *Parafoveolar Fixation:* The star is fixated steadily but rests slightly to one side of the foveola.

C. *Paracentral Fixation:* The star is fixated steadily but rests a little further to one side (at the edge of the granular, avascular area which is regarded ophthalmoscopically as the macula).

D. *Eccentric Fixation:* The star is fixated steadily and usually at a point between the foveola and the disk, but it may even rest on the disk itself or to the nasal side.

E. *Wandering Fixation:* There is no steady fixation; the star wanders in an irregular fashion over the area between the foveola and the disk but is not located in one spot.

This classification has been discussed more fully by Graham (1961). Since many of the children examined were very young it was difficult to assess parafoveolar fixation accurately, and for the purpose of this paper the few cases in which this type of fixation was diagnosed have been included with those of the paracentral type.

The non-squinting eye was examined first as a routine in order to familiarize the child in seeing the star and in recognizing it later with the other eye; to form an estimate of the powers of attention of the child; and, finally, to satisfy the examiner that central fixation was reliably present in the "good" eye. If the fixation in the non-squinting eye was not steady and central, but showed a tendency, through lack of attention, to move from the foveola then the fixation in neither eye was recorded. Inevitably there were some very young children in whom a record was unobtainable because they were crying, or struggling, or showed no tendency to co-operate.

At the same visit the sex, type of squint (unilateral-convergent, alternating-convergent, or divergent), family history of squint, age at onset of squint, interval of time between onset of squint and first examination, and any possible cause (usually an illness is given as a precipitating factor) were all noted.

## Results

A total of 512 patients were seen during the 12-month period from September, 1959, to August, 1960, at the Manchester Royal Eye Hospital. Of these, 72 had alternating convergent squint and 21 had divergent squint; in all of those in whom the fixation was recorded it was found to be central. Among the remaining 419 patients with unilateral convergent squint there were 76 in whom the fixation was not recorded for the reasons mentioned above, and in a further 39 other data—for example, history, refractive error—were incomplete. A total of 304 patients with unilateral convergent squint therefore remained for further analysis. 68 of these had non-central fixation of the following types: 13 unsteady central, 9 paracentral, 35 eccentric, and 11 wandering.

The relationship between the incidence, sex, family history, presence of a possible cause, and the eye affected is shown in the Table. None of these factors had a statistically significant effect on the incidence.

*Incidence of Non-central Fixation According to Various Factors*

| Fixation | Sex | | Family History | | Cause Ascribed | | Eye Affected | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | M | F | Yes | No | Yes | No | R.E. | L.E. | |
| Central .. | 122 | 114 | 112 | 124 | 98 | 138 | 107 | 129 | 236 |
| Non-central | 32 | 36 | 36 | 32 | 26 | 42 | 36 | 32 | 68 |
| Total .. | 154 | 150 | 148 | 156 | 124 | 180 | 143 | 161 | 304 |

The relationship between the age at the time of first examination and the incidence is of no statistical importance (Fig. 2), but a scrutiny of the age at onset of the squint shows that the incidence of non-central fixation is highest in the lower age-groups (Fig. 3). Similarly, the incidence is lowest in those children who attended at an early date after the onset of the squint (Fig. 4). In ascertaining the influence of anisometropia (Fig. 5), the meridian with the greatest refractive error

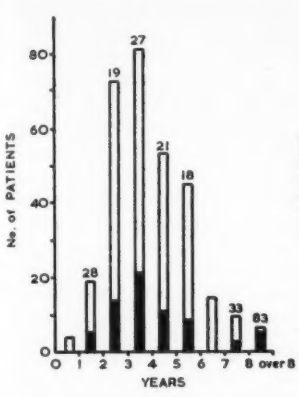



FIG. 2

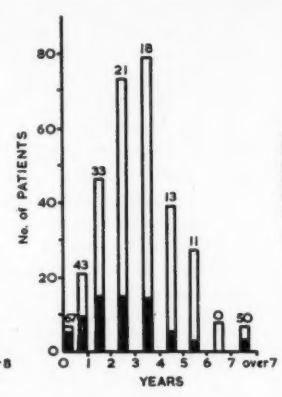



FIG. 3

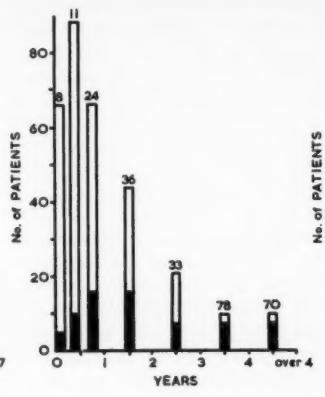



FIG. 4

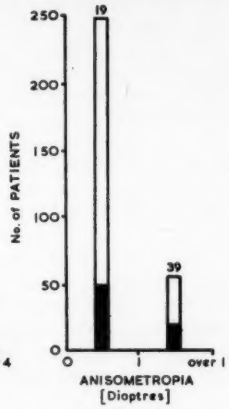



FIG. 5

FIG. 2.—Incidence of non-central fixation according to age at first examination. FIG. 3.—Incidence of non-central fixation according to age at onset of squint. FIG. 4.—Incidence of non-central fixation according to interval between onset of squint and first examination. FIG. 5.—Incidence of non-central fixation according to amount of anisometropia. In Figs. 2–5 and 9 the shaded areas show numbers with non-central fixation; figures above each column show percentage incidence.

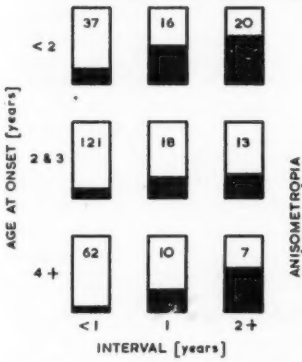



FIG. 6

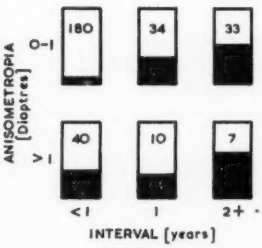



FIG. 7

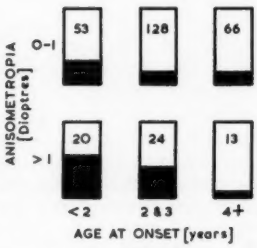



FIG. 8

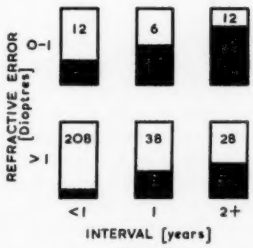



FIG. 10

FIG. 6.—Incidence of non-central fixation according to interval and age at onset of squint. FIG. 7.—Incidence of non-central fixation according to interval and degree of anisometropia. FIG. 8.—Incidence of non-central fixation according to age at onset of squint and degree of anisometropia. FIG. 10.—Incidence of non-central fixation according to interval and refractive error of fixing eye. In Figs. 6–8 and 10 the shaded areas show percentage incidence; figures in each block show total number of patients concerned.

in each eye was used for the purpose of deciding the degree of anisometropia; patients with one dioptre or less of anisometropia were regarded as having low anisometropia and those with more than one dioptre as having high anisometropia. This division has been found to correspond best with the incidence of amblyopia (Stevens, 1960). It will be seen that there is a highly significant tendency for high anisometropia to be associated with non-central fixation.

Further analysis was undertaken to see if the three significant factors of age at onset, interval, and anisometropia were independent. The relationship between the age at onset and the interval is shown in Fig. 6. It will be seen that in each age-at-onset group there is an increase in the incidence of non-central fixation as the interval between onset and examination increases. The relationship between interval and anisometropia is shown in Fig. 7; the influence of interval is again considerable in both groups of anisometropia; generally, the patients with a high anisometropia have a higher incidence than those with low anisometropia. The relationship between age at onset and anisometropia is shown in Fig. 8. The influence of anisometropia is again clear, and there is also a suggestion that the age at onset is a factor of importance. Preliminary analysis of the larger numbers of patients from the school ophthalmic clinic substantiates the view that these three factors are independent, the interval and degree of anisometropia being of particular importance.

In a series such as this, in which the fixation was assessed at first examination, it is impossible adequately to correlate it with the type of squint present, but an idea of the accommodative effort required by the child can be obtained from the refractive condition of the fixing eye, assessed as the average refractive error of the two principal meridians. Fig. 9 shows that it is

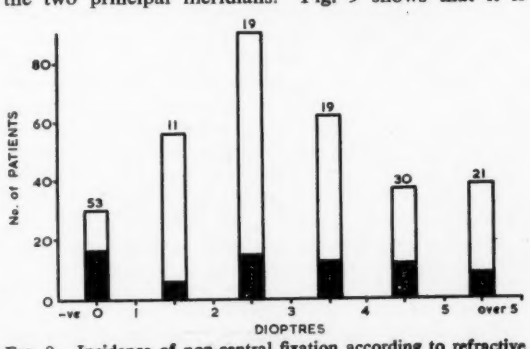



FIG. 9.—Incidence of non-central fixation according to refractive error of fixing eye.

only in the group of low refractive error (which includes two cases with a low myopic correction) that there is an appreciable excess of non-central fixation; this suggests that it is the non-accommodative squints that tend to have non-central fixation when first examined. Analysis of the interval between onset and first examination of these cases (Fig. 10), however, shows that a greater proportion of the patients with low refractive error attended in the later interval groups, and it appears, therefore, that the apparent increase in non-central fixation in these patients may be due to this relatively long interval before attendance. Once again the association of a long interval with increased incidence of non-central fixation is shown in both refractive groups. There was no significant association in this series between the refractive error and either the age at onset or the degree of anisometropia.

## Discussion

The overall incidence of non-central fixation (22.4%) found in this series of young patients with unilateral convergent squint indicates that this defect in fixation constitutes a considerable factor in the management of the amblyopia of squint.

The analysis in this paper has shown that one of the main factors influencing the incidence of non-central fixation is the interval between the onset of the squint and the time of first examination; if this interval is short, there is a low incidence of non-central fixation. This has been confirmed by a similar analysis of the patients attending the school clinic, which will be published elsewhere (Scully, 1961). Moreover, evidence is accumulating to suggest that if occlusion treatment can be instituted early it may result in a re-establishment of central fixation, whereas it is generally agreed that well-established non-central fixation will not respond to such simple measures. Treatment, which can be instituted only at an age of not less than 7 years, is by complex methods involving projection of after-images (Cüppers, 1956), or direct stimulation of the macula (Bangerter, 1953). This treatment may require from 30 to 120 attendances and is expensive both in the time spent by the patient and in the personnel and facilities required. The prevention of non-central fixation is therefore clearly desirable.

The interval between onset and examination on which the incidence of non-central fixation is so clearly dependent is a factor largely under the control of the family doctor. Since this factor appears to be independent of the others it is reasonable to assume that if all patients could be seen with the minimum of delay after the onset of squint the incidence of non-central fixation would be very much smaller. It cannot be emphasized too strongly that as soon as a child is seen to squint it should be referred for examination. This applies to infants, to the toddlers of pre-school age, and to children of school age. There should be no hesitation in referring the child on the grounds of age or of the intermittency of the squint. Early treatment can then result in a saving of much time and energy on the part of both the ophthalmic specialist and the orthoptic department, as well as a considerable economic saving to the patient's family.

## Summary

A survey of the incidence of non-central fixation, which is associated with one of the more intractable forms of amblyopia, in children with squint attending an eye hospital for the first time shows that a short interval between the onset of squint and attendance for examination is associated with a low incidence of non-central fixation. The incidence is also low in those patients with a late age of onset and in those with a low degree of anisometropia. These findings are similar to those in a parallel series attending a school clinic.

It is concluded that referral of children with squint to a hospital eye department or school ophthalmic clinic as soon as the squint is noticed can be expected to minimize the incidence of non-central fixation, and therefore to make a major contribution to the prevention of loss of vision.

We are indebted to the surgeons of the Manchester Royal Eye Hospital for allowing us to investigate these patients under their care, and we gratefully acknowledge the helpful criticisms of Dr. A. Stanworth, Reader in Ophthalmology, University of Manchester, in the preparation of this paper.

### REFERENCES

Bangerter, A. (1953). *Ophthalmologica (Basel)*, **125**, 398.
Cole, R. B. W. (1959). *Brit. med. J.*, **1**, 202. Editorial comment, p. 221.
Cüppers, C. (1956). *Klin. Mbl. Augenheilk.*, **129**, 579.
—— (1958). "Orthoptic and Pleoptic Problems in Germany." Lectures to the North of England Ophthalmological Society, June 12 and 13, 1958.
Graham, P. A. (1961). *Brit. orthopt. J.* In press.
Naylor, E. J., and Wright, A. G. (1959). Ibid., **16**, 109.
Von Noorden, G. K. (1960). *Amer. Orthopt. J.*, **10**, 7.
Scully, J. (1961). *Brit. J. Ophthal.* In press.
Stevens, P. R. (1960). *Brit. orthopt. J.*, **17**, 66.

# ERYTHEMA MULTIFORME AND NEPHRITIS

BY

**J. S. COMAISH, M.B., M.R.C.P.**
*Registrar, Department of Dermatology*

AND

**D. N. S. KERR, M.B., M.Sc., M.R.C.P. M.R.C.P.Ed.**
*First Assistant, Department of Medicine*

*From the Royal Victoria Infirmary, Newcastle upon Tyne, and King's College Medical School, University of Durham*

Erythema multiforme is a reaction of the skin and mucous membranes to various agents, among them drugs such as the sulphonamides, codeine, and the hydantoins. It is seen fairly often in dermatological practice in this country, and is characterized by erythema (which may assume the classical "target figure" form), purpura, and sometimes vesicles and bullae. There is usually systemic upset with fever and malaise, and in the severe form (so-called Stevens–Johnson syndrome) the mucous membranes of the mouth, eyes, and genitalia may be affected. Histologically there is a cellular infiltrate, particularly around the dilated vessels, with oedema of the dermis and prickle-cell layer, which may proceed to vesicle formation. Certain infections, especially streptococcal, may precede erythema multiforme, and some investigators maintain that the common recurrent type is a hypersensitivity reaction to streptococci (Welsh, 1948). Most dermatologists do not accept this view, and many think a viral cause more likely. Herpes labialis is a common accompaniment of erythema multiforme,

and the herpes simplex virus has been isolated on occasion both from vesicles (Foerster and Scott, 1958) and from the lungs (Finland *et al.*, 1948).

That organs other than the skin may be affected has long been recognized, and special attention has been paid to the pulmonary complications. Few observers, however, have recorded nephritis in this condition, and the majority seem unaware of such an association. Von Hebra (1866) did not include visceral complications other than pneumonia in his early description. The otherwise comprehensive review of the Commission on Acute Respiratory Diseases (1946) stated that "nephritis is not known in this syndrome." None of the standard textbooks of dermatology or general medicine mention nephritis in this condition. Lever (1944) stated that "no renal involvement occurs save transient albuminuria." Ashby and Lazar (1951) reported four cases of erythema multiforme and reviewed the literature to that date but did not mention nephritis.

Osler (1888, 1900), however, was at pains to emphasize nephritis as a serious complication in 6 of his 16 cases of "erythema multiforme." Later authors pointed out the diversity of these cases, and Osler (1914) himself later agreed that some (but not all) were certainly examples of Schönlein–Henoch syndrome. Nephritis is a well-recognized complication of this syndrome (Gairdner, 1948).

Scattered reports since Osler's time record features which indicate renal involvement in some patients with erythema multiforme. Costello (1947) described the case of a man of 36 with severe erythema multiforme whose urine contained a large amount of albumin. At necropsy the kidneys showed the following: "Extensive severe finely granular degeneration, bordering on necrosis. There were areas of interstitial oedema. Large hyaline casts were present in a number of collecting tubules. Many small arterioles, especially the afferent, show hyalinization of the walls, but only a few obliterated capillaries are seen. The glomerular tufts were congested. The walls of the capillaries were thick, of 'wire loop' type, but patent and not fused. Occasional protein was present in the glomerular capsule." There is no record of a blood-urea estimation in life.

Another of Costello's patients, a woman of 25, had frank haematuria and her urinary deposit contained casts and leucocytes. Robinson and McCrumb (1950) described 11 cases, 2 with severe albuminuria; one developed oedema and died. He did not record blood-urea estimations or other renal investigations. Ustvedt (1948) in his review reported the case of a boy of 10 years with severe erythema multiforme who developed acute nephritis. He had haematuria, and cylindruria, and a blood-urea level of 86 mg./100 ml. but his blood-pressure was normal. Levitt and Burbank (1953) described the case of a man of 58 with bilateral pulmonary tuberculosis who developed purpuric lesions after an injection of penicillin for pharyngitis, which later became haemorrhagic. The skin lesions progressed to bulla formation. Signs of nephritis then appeared; the urine contained visible blood, albumin, and casts, and the blood urea rose to 100 mg./100 ml. The patient died of pulmonary tuberculosis. Levitt and Burbank listed the case as Schönlein–Henoch syndrome; but in view of the patient's age, the bullous lesions, and the severe haemorrhagic pharyngitis, the description more closely resembles the purpuric form of erythema multiforme.

Dresner (1949) reported the case of a man of 27 with severe erythema multiforme who had heavy albuminuria for 21 days, with occasional red blood cells and leucocytes in the urinary deposit. There was no balanitis or urethral discharge and the urine was sterile throughout.

Many other individual case reports mention albuminuria, and occasionally haematuria, but do not record urine microscopy or blood-urea levels. It is clear that little significance is usually attached to albuminuria in this condition and that it rarely leads to fuller investigation, even in the most severe cases. Perhaps the vague term "febrile albuminuria" has diverted attention away from this important finding.

That renal involvement may occur in erythema multiforme, and be an early and serious feature affecting prognosis, is illustrated by the following case reports.

### Case 1

A housewife of 58 was admitted to the Royal Victoria Infirmary on February 10, 1960. She had been well until seven days previously, when she developed soreness of the eyes and mouth. On the next day lesions appeared in the mouth and on the eyelid margins, and, on the day after, an erythematous macular eruption occurred, spreading rapidly over the whole body. She developed haematuria, dysuria, cough, sputum, and haemoptysis. She had taken no drugs prior to the onset of the illness.

On examination she was an obese, ill-looking woman virtually covered with the typical rash of erythema multiforme. In many areas the classical target figures predominated, but in others there were purpuric lesions. Friction had removed the top layers of the skin from coalescing lesions, leaving raw denuded areas. Erosions were present on the lid margins and in the nose, mouth, and vulva, with bleeding and crusts. The blood-pressure was 140/80 mm. Hg. Scattered rhonchi were heard in the chest. Her urine was smoky and there was moderate albuminuria. Numerous red cells and leucocytes were present in the deposit, and coliform organisms were cultured from a clean midstream specimen. Her blood urea was 30 mg./100 ml.; plasma electrolytes were normal; the serum albumin was 3.1 and globulin 3.1 g./100 ml., with a well-marked increase in $\alpha_2$ globulin on electrophoresis. Chest *x*-ray examination was negative, but pneumococci and staphylococci were cultured from her sputum.

Treatment with dexamethasone 1 mg. six-hourly and tetracycline 250 mg. six-hourly was started on February 15. The blood urea rose to 198 mg./100 ml. by February 23. Plasma potassium rose to 6.9 mEq/l. the same day, and treatment with resonium A was necessary. Her skin condition improved, but ankle oedema appeared, albuminuria persisted, and the blood urea continued to rise. On February 27 she suddenly complained of violent abdominal pain, became cyanosed, and died within 10 minutes. Permission for necropsy was refused.

### Case 2

A housewife of 42 was admitted to the Ipswich and East Suffolk Hospital on November 23, 1958. Her past history had been uneventful and her blood-pressure and urine examination were normal at an obstetric examination in 1952. She had felt vaguely unwell for six weeks, and three weeks before admission had left-sided abdominal pain, followed the next day by the appearance of red spots over the arms and legs. The skin lesions evolved with the formation of blisters, some with blood in them, and pains occurred in several joints. She was seen on November 20 by a dermatologist (Dr. J. B. Lyon), who diagnosed erythema multiforme. The mucous membranes were not involved. There was no history of drug-taking apart from occasional aspirin tablets. Her pulse was 100, but her temperature,

Hb, W.B.C., E.S.R., and chest *x*-ray films were normal. On November 22 she developed severe diarrhoea, which led to her admission the next day to a medical ward, under the care of Dr. J. W. Paulley.

On examination on November 23 she had a rash on her legs, arms, wrists, and face, and looked ill. There were some petechiae, but the predominant lesions were haemorrhagic bullae, with some secondary infection, and a diagnosis of erythema multiforme was again recorded. This was confirmed by skin biopsy, on which Dr. A. B. Lintott reported: "The skin lesion is a subepidermal bulla containing fibrin, polymorphs, and red cells. There are patchy areas of extravasation of red cells into the dermis at the edge of the bulla. There is a patchy perivascular inflammatory exudate, consisting of lymphocytes and neutrophils, in the neighbourhood of the lesion. Only scanty eosinophils are seen. Histologically this is bullous erythema multiforme."

Her urine contained albumin (70 mg./100 ml.) and a small number of hyaline and granular casts; it was sterile. Blood urea was 40 mg./100 ml., serum albumin 3.2 and globulin 3.5 g./100 ml., with increase in $\alpha_1$-, $\alpha_2$-, and $\beta$-globulins on electrophoresis. The antistreptolysin (A.S.O.) titre was 100 units/100 ml. Her stool contained occult blood persistently, but bleeding and clotting times and platelet count were normal. Muscle biopsy was normal.

Treatment with prednisone 10 mg. eight-hourly was begun on November 29, but the rash spread, and by December 1 involved her buttocks, back, and palate. A throat swab yielded Vincent's organisms only. On December 12 her urine contained albumin, hyaline casts, red cells, and leucocytes; A.C.T.H. was added to the therapy. By December 15 the rash and abdominal pain was clearing, and blood urea had fallen to 35 mg./100 ml., but she then developed a nephrotic syndrome with albuminuria of 12 g./l., serum albumin 1.9, globulin 2 g./100 ml., and moderately severe oedema of legs and sacrum. Blood urea rose again to a maximum of 160 mg./100 ml. on January 1, 1959. Blood-pressure readings were consistently normal.

Withdrawal of corticosteroids on January 5 was followed by a brisk diuresis and a fall in blood urea to 32 mg./100 ml. by January 19. Oedema and albuminuria disappeared and her general condition improved. She has been followed since discharge, and there have been no further symptoms referable to skin or urinary tract. When last seen (November 30, 1960) she was well, and the blood urea, Hb, and E.S.R. were all normal.

## Case 3

A man of 63 was admitted to Addenbrooke's Hospital on December 8, 1959. He was receiving digitalis and mersalyl consequent upon a myocardial infarction four years previously, and took an ipecacuanha mixture for chronic bronchitis. There was no history of recent infection or the administration of other drugs. Six days before admission he developed a rash on his thighs and face, spreading to the trunk. Two days later lesions appeared in the mouth. His temperature was 99° F. (37.2° C.), B.P. 95/70 mm. Hg, and some crepitations were present at both bases. The typical rash of erythema multiforme was present, but glans and urethra were not involved.

There was moderate albuminuria and some granular casts were found in the deposit. Blood urea was 104 mg./100 ml., E.S.R. 33 mm./hr., Hb 13.2 g./100 ml., and W.B.C. 11,000/c.mm. Electrophoresis showed relative increase in $\alpha_2$- and $\gamma$-globulins. There was mottling of the right lower zone on the chest *x*-ray film. Pathogens were not grown from a throat swab, but A.S.O. titre was 320 units/100 ml.

He recovered without treatment, and the blood urea fell to 48 mg./100 ml. five days later.

## Case 4

A housewife was first seen at the Royal Victoria Infirmary in 1949, when she underwent lobectomy for localized bronchiectasis. Her mother had suffered from severe rheumatoid arthritis, and the patient herself developed typical widespread rheumatoid arthritis in 1948, when aged 32. Her joint symptoms continued to trouble her until the start of prednisone therapy in 1960. The diagnosis was later confirmed by the development of characteristic deformities, rheumatoid nodules, and a positive (1:128) Rose–Waaler test. Her treatment to 1956 included salicylates and four courses of sodium aurothiomalate ("myocrisin"). She was treated with low doses of prednisone and supplementary injections of corticosteroids into individual joints on a number of occasions between 1956 and 1960. A skin rash was noted on the forearms when she attended the rheumatoid clinic in February, 1959, and this led to a search for lupus erythematosus (L.E.) cells in the blood. L.E. cells were not found then, nor on six subsequent occasions over the next 18 months. The E.S.R. was persistently raised to about 90 mm./hr. Her blood-pressure was normal (140/75 mm. Hg), and albuminuria was not detected at an examination in February, 1959.

On October 4, 1959, she was referred to the skin department and seen by Professor J. T. Ingram on account of an eruption on her face, lips, arms, legs, and inside the mouth, which was diagnosed as severe erythema multiforme. She gave a history of similar attacks recurring every few months over the preceding two years. She was seen again by Professor Ingram on December 2, when a further attack with sore throat occurred two weeks after an intra-articular injection. The eruption was a typical widespread erythema multiforme. She gave a history of the development of mouth ulcers, without skin rash, at a similar interval after previous injections. Her blood-pressure was 140/100 mm. Hg., Hb 9.2 g./100 ml., and electrophoresis showed a well-marked increase in $\alpha_2$- and $\gamma$-globulins. Another intra-articular injection of prednisone was given in August, 1960, after preliminary skin-testing. In spite of a negative intradermal test, further eruption appeared three weeks later. On this occasion she was found to have moderate albuminuria, a blood urea of 104 mg./100 ml., and a blood-pressure of 210/120 mm. Hg, and was admitted to the medical unit under Professor G. A. Smart for further investigation.

Her rash faded soon after admission to hospital, but the blood urea remained above 100 mg./100 ml., and the albuminuria and the presence of red cells and leucocytes in the urinary deposit persisted. There was no splenomegaly, and the white blood cell count was normal on several occasions. Needle biopsy of the kidney (Fig. 1) showed sclerosis of many glomeruli, crescent formation, and round-cell

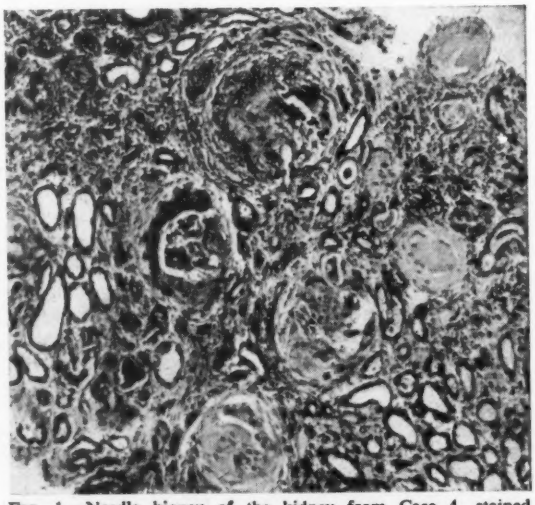


FIG. 1.—Needle biopsy of the kidney from Case 4, stained haematoxylin and eosin, showing crescent formation and destruction of glomeruli. (×100.)

infiltration of the periglomerular interstitial tissue. The typical "wire loop" lesions of advanced lupus nephritis were not seen, and stains for amyloid were negative. Culture of blood from the biopsy needle was sterile, but coliform organisms were grown from the post-biopsy midstream urine.

She was treated with an increased dose of prednisone (30 mg./day) which caused a dramatic improvement in her arthritis. During the six-months follow-up the albuminuria has been reduced to a faint trace (30 mg./100 ml.), the urinary deposit has returned almost to normal, but no reduction in the blood-urea level or blood-pressure has occurred. During September, 1960, her prednisone dosage was temporarily reduced because of side-effects, and during this period the rash recurred. On this occasion there was no vesiculation, and a skin biopsy showed endothelial swelling of arterioles and extravasation of red blood cells and leucocytes into the upper dermis similar to that found in anaphylactoid purpura.

### Case 5

A housewife of 59 was first seen in the skin department of the Royal Victoria Infirmary on October 17, 1960, with a history of recurrent attacks of erythema multiforme for five years after an attack of shingles. The episodes lasted two to three weeks, and were separated by intervals of about six weeks. Her urine did not contain albumin, and was normal on microscopy. She returned on October 28 during a typical attack, with target lesions on the skin and ulcers on the tongue. Her urine contained a trace of albumin. Haemolytic streptococci of Lancefield group A were cultured from a throat swab. Her Hb and white cell count were normal, E.S.R. 25 mm./hr., blood urea 41 mg./100 ml. She was treated with sulphamethoxypyridazine 0.5 g. daily, but the rash spread, her temperature rose to 101° F. (38.3° C.), and she was admitted on November 7.

On admission she looked ill, but physical examination was normal apart from the rash, which had spread and become confluent in some areas on the limbs, face, and trunk. The fauces were reddened, but there was no ulceration of the mouth or vulva. Her blood-pressure was 130/80 mm. Hg. Her urine contained moderate amounts of albumin, many red cells, and some leucocytes and granular casts. Basal crepitations were noted on November 8, but the chest *x*-ray picture was normal and she had no cough or sputum. Prednisone 10 mg. eight-hourly was begun on November 11, and within 24 hours her rash was fading and her temperature had settled to normal. The urine output remained reasonable (about 800 ml./day), but she became breathless and developed oedema, pleural effusions, and raised venous pressure. The heart was not significantly enlarged, and E.C.G. was normal. The blood urea had risen to 103 mg./100 ml. and plasma sodium had fallen to 119 mEq/l. by November 12. On the 16th, when her blood urea was 250 mg./100 ml., she was transferred to the artificial kidney unit and treated with the standard conservative regime of low-protein diet and fluid restriction (Elliott *et al.*, 1960). The same day she developed signs of a right-lower-lobe pneumonia, and a resistant staphylococcus was isolated from her sputum. Tracheotomy was required next day for severe respiratory distress. She improved after a haemodialysis on November 20 and passed into the early diuretic phase of acute renal failure, but she died of a further exacerbation of her chest infection on November 27.

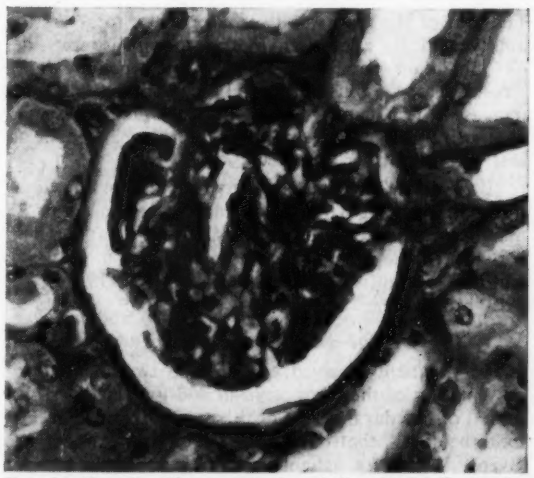


FIG. 2.—Case 5. Kidney stained periodic-acid Schiff, showing acute tubular damage and adhesion of glomerulus to Bowman's capsule. Specimen taken with biopsy needle 10 minutes after death. (×360.)

Necropsy revealed severe tracheobronchitis and pneumonia, venous congestion, and large pale kidneys with prominent glomeruli. On microscopy (Fig. 2) there were degenerative changes in the convoluted tubules typical of "acute tubular necrosis," and some glomerular changes not typical of that condition. There was some increase in the cellularity of glomeruli with reduction in capillary lumina and adhesions between capillary loops and Bowman's capsule. There was no crescent formation or cellular infiltration of the type seen in Case 4.

### Discussion

The only satisfactory classification of disease is one based on aetiology. Erythema multiforme is a skin reaction which is clinically distinct but of multiple aetiology; in other words, it is a syndrome, not a disease. We believe that this syndrome is associated with a renal lesion more commonly than is generally realized. Four of the five cases described were seen by one of us (J.S.C.) during two years of mixed general medical and dermatological practice. It is our impression that in the past the possibility of renal complications has not been sufficiently appreciated, and consequently full urine examination and blood-urea estimation have seldom been performed. Albuminuria, when present, has usually been attributed to fever or local lesions of the urethra and surrounding structures. Only one of our patients (Case 1) had urethral involvement; this could not in any case account for the uraemia.

Both the clinical features and the histological abnormalities in our patients may be found in a number of different diseases involving the kidneys. We have therefore considered the possibility that our patients were suffering coincidently from the rash and unrelated renal diseases. The close association in time between the dermal and renal manifestations makes this very unlikely. Ascending urinary infection might be expected to accompany erythema multiforme in some patients with genital involvement, and a positive culture was in fact obtained from a midstream urine specimen in the one patient with vulval lesions. However, none of our patients had the typical clinical or histological features of urinary infection, and none had pyuria. The positive culture immediately after biopsy in Case 4 is of unknown significance; we have found this in several patients with glomerulonephritis. Several other possible causes of renal damage were suggested by the history in Case 4; however, amyloid was excluded histologically and systemic lupus erythematosus is unlikely in view of the persistently negative L.E. cell test. The urine and blood-pressure were known to be normal three years after her last course of gold injections, and her renal abnormalities appeared after the onset of her rash.

If erythema multiforme is indeed a result of streptococcal infection in a substantial proportion of cases, it

would be surprising if it were not sometimes associated with acute glomerulonephritis. The association would not necessarily be very frequent. Acute glomerulonephritis has a different age incidence,, and in this country it almost always follows infection with a single type of streptococcus (type 12). Erythema multiforme may well be a reaction to infection with many different types of streptococci, as rheumatic fever seems to be. Streptococci of group A were isolated from the throat of one of our patients and another had a raised A.S.O. titre as evidence of preceding streptococcal infection. On the other hand, none of our cases followed the typical course of acute glomerulonephritis ; three were normotensive or hypotensive throughout and none had hypertension early in the illness ; no patient had a classical onset with headache, generalized oedema, frank haematuria, and oliguria. These observations apply also to the previously described patients referred to in the introduction. It has been said that acute glomerulonephritis often follows an atypical course in older adults, but this may simply imply that there are several different renal diseases referred to by this title at present (Hall *et al.*, 1961).

The histological changes in Case 4 (Fig. 1) are similar to those in the progressive type of acute glomerulonephritis (Ellis, 1942), but are not specific to this condition ; they have been described in lupus nephritis (Muehrcke *et al.*, 1957) and in the Schönlein–Henoch syndrome (Heptinstall, 1960). The changes in the glomeruli in Case 5 (Fig. 2) are non-specific.

There were some clinical similarities to Schönlein–Henoch syndrome ; two of our patients complained of abdominal pain, and one had persistent occult bleeding from the bowel and transient arthralgia, but the rash in all our patients was unmistakably that of erythema multiforme.

Four of our cases were treated with corticosteroids ; in three the skin rash resolved within a few days of the beginning of therapy and in one it recurred during temporary reduction in steroid dosage. Improvement in the renal condition, when it occurred, was less dramatic and slower ; it may well have been coincidental.

We conclude that an inflammatory renal lesion with some similarities to acute glomerulonephritis accompanies erythema multiforme in a proportion of cases ; that it may lead to fatal uraemia during the acute illness ; and that recurrent episodes may produce chronic nephritis. Further study—clinical, bacteriological, and histological—will be required to determine whether the lesion is identical with acute glomerulonephritis after streptococcal infection. The results may well be important in determining whether long-term prophylactic penicillin is indicated in patients with recurrent attacks.

### Summary

Five cases are described in which erythema multiforme was accompanied by the onset of a form of nephritis manifested by albuminuria, microscopical haematuria, cylindruria, and uraemia. Hypertension and oliguria were not features of the acute attack.

Two patients died during the acute attack, one progressed to subacute nephritis with chronic uraemia, one developed a nephrotic syndrome and subsequently recovered, and in one the renal abnormalities subsided with the rash.

The histological features in two cases are described.

We are indebted to Professor J. T. Ingram, Professor G. A. Smart, Dr. J. W. Paulley, Dr. G. I. Holti, Dr. A. Rook, and Dr. M. Thompson for their help and encouragement.

### References

Ashby, D. W., and Lazar, T. (1951). *Lancet*, **1**, 1091.
Commission on Acute Respiratory Diseases (1946). *Arch. intern. Med.*, **78**, 687.
Costello, M. J. (1947). *J. invest. Derm.*, **8**, 127.
Dresner, E. (1949). *Lancet*, **2**, 1036.
Elliott, W., Hill, M., Kerr, D. N. S., and Ashcroft, R. (1960). *Postgrad. med. J.*, **36**, 230.
Ellis, A. (1942). *Lancet*, **1**, 1.
Finland, M., Jolliffe, L. S., and Parker, F., jun. (1948). *Amer. J. Med.*, **4**, 473.
Foerster, D. W., and Scott, L. V. (1958). *New Engl. J. Med.*, **259**, 473.
Gairdner, D. (1948). *Quart. J. Med.*, **17**, 95.
Hall, M., Kerr, D., Smart, G., Ashcroft, R., Elliott, W., and Swinney, J. (1961). *Brit. J. Urol.*, **33**, 41.
Hebra, F. (1866). *On Diseases of Skin*, vol. 1, p. 285. New Sydenham Society, London.
Heptinstall, R. H. (1960). In C. V. Harrison's *Recent Advances in Pathology*, 7th ed. Churchill, London.
Lever, W. F. (1944). *Arch. Derm. Syph. (Chicago)*, **49**, 47.
Levitt, L. M., and Burbank, B. (1953). *New Engl. J. Med.*, **248**, 530.
Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E. (1957). *Medicine (Baltimore)*, **36**, 1.
Osler, W. (1888). *N.Y. med. J.*, **48**, 675.
—— (1900). *Brit. J. Derm.*, **12**, 227.
—— (1914). *Brit. med. J.*, **1**, 517.
Robinson, H. M., jun., and McCrumb, F. R., jun. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 539.
Ustvedt, H. J. (1948). *Acta med. scand.*, **131**, 32.
Welsh, A. L. (1948). *J. invest. Derm.*, **10**, 401.

## CHRONIC BRONCHITIS

### CONTROLLED TRIAL OF ISOPRENALINE AND CHYMOTRYPSIN BY INHALATION

BY

**P. O. LEGGAT, M.D., M.R.C.P.**

**C. VERITY, M.D., B.Sc., D.P.H.**

*Walker Gate Hospital, Newcastle upon Tyne*

AND

**D. J. NEWELL, M.A.**

*Department of Industrial Health, Medical School, Newcastle upon Tyne*

The aim of the trial was twofold ; firstly, to assess the ability of finely divided chymotrypsin with isoprenaline by inhalation to relieve airways obstruction ; and, secondly, to assess its ability to liquefy sputum and thus increase the quantity expectorated when presented alternatively as a fine dry powder or suspended in an inert propellant.

The patients were admitted to hospital for the duration of the trial. The clinical material consisted of 35 male patients aged 30 to 65 years. All the patients had had winter cough and sputum for at least three years, and had been off work at least once, during that period, with bronchitis.

### Method

Every patient received each of the two methods of presentation of the chymotrypsin and isoprenaline for a period of five days. Each of these periods was preceded by three days " control " during which no treatment was given. Whether a patient should start with the powder or with the suspension was determined from a list based on random numbers. None of the patients had antibiotic therapy of any kind.

Analysis of the primary objective was carried out sequentially according to one of the designs described by Armitage (1957). After 31 men had been admitted, the sequential plan indicated that the trial should stop. At this stage a further four men were already receiving treatment. The trial was then continued until these men had completed their course of treatment, no new patients being admitted.

During the trial three men had to be withdrawn from treatment (as explained later). The subsequent analysis is based on the 32 men who completed the trial.

The inert propellant suspension was presented in a pressurized ampoule with a metering valve at the outlet permitting a dose of 0.05 mg. of isoprenaline sulphate and 1 mg. of chymotrypsin to be dispensed at each operation. The dosage schedule was 0.1 mg. of isoprenaline with 2 mg. of chymotrypsin administered before breakfast, at noon, and before retiring.

The medicament powder mixture was presented in a cartridge containing 0.1 mg. of isoprenaline sulphate with 0.1 Anson unit of chymotrypsin. The powder was expelled from the cartridge by the use of a rubber bulb and a trip-valve mechanism actuated by the negative pressure of inspiration. One cartridge was used before breakfast, one at noon, and one before retiring. All specimens of sputum were collected in dry waxed containers. The weight of a 24-hour collection was recorded daily and expressed as a percentage of the average in the preceding control period.

A "Garthur expirograph" with a 9.5 L bell and a circumferential speed of 1 cm. a second was used to estimate the forced expiratory volume in the first second ($F.E.V._1$). Six estimations were carried out at the end of each control and each therapy period, and the result was expressed as a mean of six readings. In the therapy periods, at least three hours were allowed to elapse between the last dose of the medicament and the estimation of the F.E.V.

The main criterion used in the sequential analysis of the trial was the percentage improvement in the $F.E.V._1$ after taking chymotrypsin and isoprenaline for five days as compared with that in the preceding control period. For each patient the decision "better with powder" (or suspension) was made if the percentage improvement was more than 10% greater for one than the other—for example, a patient who improves his $F.E.V._1$ by 20% with the suspension would only be regarded as "better with powder" if his improvement with it was at least 30%. This order of difference was decided on clinical grounds; smaller differences were allocated to a group "same on both treatments."

As already stated, the $F.E.V._1$ was measured before the chymotrypsin–isoprenaline treatment was given with either the powder or suspension. Each of these readings gave a baseline for comparison with readings taken at one minute, three minutes, three hours, and six hours after the corresponding treatment was given. Improvements in the $F.E.V._1$ at these times were calculated as percentages of the relevant baseline figure.

## Results

The particular sequential chart used had the following properties:

If the two treatments were equally effective in improving the F.E.V. after five days' therapy there was only a 1 in 20 chance of wrongly concluding that one of them was better.

There should not be more than 30 patients in the trial who were "better"—that is, had a 10% greater improvement—on one form of administration than the other. While this does not set an exact limit on the total number of patients in the trial, it does impose some restriction on the number which, in any case, seemed reasonable in terms of the available hospital clinical resources.

If one form of administration was so good that 85% of patients with a preference were "better" on that treatment, there would only be a 1 in 20 chance of not recognizing that it was better.

With the criterion of improvement used, 12 out of 32 patients were the same on both treatments. By the time the boundary of the Chart was reached, 16 men had been better on one form of administration than the other; these were equally divided into eight better with the powder and eight better with the suspension. The conclusion from the sequential trial is that there was no significant difference between the two forms of administration. The results after five days on each treatment, in all 32 men, are shown in Table I.

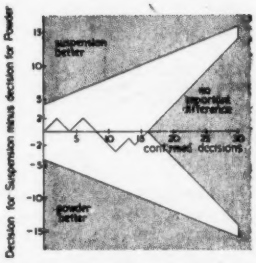



Chart showing results of sequential trial.

To answer the question whether either form of administration improved the $F.E.V._1$, comparisons were made with the corresponding values for the control periods in all 32. For the suspension, the average improvement after five days' treatment was +2.6% with a standard error of 3.5%. For the powder, the results after five days' treatment were slightly worse than before treatment, the average improvement being −0.9% with a standard error of 3.3%. In neither case is the result significantly different from zero. In other words, we have no evidence to suggest that chymotrypsin and isoprenaline sulphate mixture produces a long-term increase in the $F.E.V._1$ by whichever method it is administered.

Sputum weights were on the average decreased during treatment with isoprenaline and chymotrypsin, although not significantly so. With the suspension, results were 6.6% lower than control (standard error 4.3%) and with the powder, 2.1% lower than the control (standard error 6.6%). The difference between these results, 4.5%, had a within-patient standard error of 7.3%, and this was not significant.

The immediate effect of treatment on the $F.E.V._1$ is summarized in Table II. At one minute both methods of administration improve the $F.E.V._1$ by 17.4% and 14.7% respectively; these two figures do not differ significantly. At three minutes the improvements are slightly greater, at 18.5% and 18.1%. Thus chymotrypsin and isoprenaline initially increase the $F.E.V._1$

TABLE I.—*Results in 32 Men After Five Days of Treatment*

| | Suspension | Powder |
|---|---|---|
| Average $F.E.V._1$ before treatment .. | 1·08 litres | 1·13 litres |
| Average percentage improvement .. | +2·6% | −0·9% |
| Standard error .. .. .. .. | 3·5% | 3·3% |
| Average sputum weight before treatment .. | 37·1 g. | 37·7 g. |
| Average percentage increase .. .. | −6·6% | −2·1% |
| Standard error .. .. .. .. | 4·3% | 6·6% |

to a significant and marked extent, but the mode of administration is immaterial. By three hours after treatment, however, results are on the average just the same as before treatment; by six hours after treatment the F.E.V.$_1$ is actually lower in the 32 men than before treatment, but not by a significant amount.

In those patients who had never used chymotrypsin before the trial there was no evidence of any immediate toxic reactions. Four patients, however, had to discontinue therapy within four weeks and one within 12 weeks of starting; in the four cases there was a marked increase in the breathlessness and wheezing closely associated with the inhalation of the medicament.

TABLE II.—*F.E.V.$_1$ After Treatment*

| | Suspension | Powder |
|---|---|---|
| Average F.E.V.$_1$ before treatment .. | 1·12 litres | 1·15 litres |
| ,, percentage increase at 1 minute .. | 17·4±3·6 | 14·7±2·5 |
| ,, ,, ,, ,, 3 minutes | 18·5±3·8 | 18·1±2·5 |
| ,, ,, ,, ,, 3 hours .. | 0·1±3·0 | −0·1±1·9 |
| ,, ,, ,, ,, 6 ,, .. | −0·8±3·0 | −4·7±2·5 |

The remaining patient developed a very hoarse voice accompanied by a very dry irritating cough which made sleep almost impossible. One patient had to be taken out of the trial while in hospital. He became acutely breathless on starting the therapy, and his forced vital capacity (F.V.C.) decreased by half. A further attempt at inhalation in this individual, using half the previous dose of chymotrypsin without isoprenaline sulphate, produced an immediate fall in the F.V.C., but not to such an alarming extent. On further questioning it became apparent that this patient had used chymotrypsin with isoprenaline for a period of six weeks, some months before entering the trial. A further patient had to be removed from the trial as he completely failed to co-operate, and a third because of an acute exacerbation of his bronchitis in the control period.

## Discussion

For therapy to be satisfactory in chronic disease it must be effective, free from toxicity, not requiring to be used frequently, and any apparatus connected with it must be reliable and easy to use. We did not find any evidence of improvement in the breathing in the long-term experiment (Table I). In the short-term experiment there was an improvement of statistical significance in the F.E.V.$_1$ at three minutes, in the case of both the powder and the suspension. However, it was of a transient nature in both instances, and had disappeared by three hours, while at six hours the F.E.V.$_1$ was worse than it had been before therapy. This rather suggests a rebound phenomenon. It has been stated by other authors that the administration of isoprenaline with an effective size of 1 to 5 mμ, in a dosage of 0.15 mg., will produce a significant increase in the F.E.V.$_1$ for one to three hours (Robinson *et al.*, 1958b), but this has not been our experience at the interval of three hours or longer. It is reasonable to suppose that if the sputum underwent liquefaction it would be coughed up more easily, and that the viscosity would be reduced and the quantity expectorated increased. Indeed, this is what has been found by Robinson *et al.* (1958a). These authors reported that in 39% of their cases the sputum was increased in quantity, and that there was evidence of reduced viscosity. We did not carry out viscosity estimations, but our results show a decrease in the average daily quantity of sputum expectorated.

In regard to the question of toxicity, we had to discontinue treatment in the long-term follow-up in five cases for what appeared to be allergic reactions. It has been recognized for some time that there is always a possibility of allergic reactions to both chymotrypsin and trypsin, although it has always been thought to be less likely to occur with the former. Cases have been reported by Maclaren and Aladjem (1957), Fullgrabe (1957), Lichtman (1957), and Liebowitz and Ritter (1960).

One of our cases developed a very severe non-specific laryngitis and tracheitis. Similar cases of hoarseness have been reported by Robinson *et al.* (1958a), although these authors make the point that the three patients in question were on a "high enzyme dosage." On the basis of subjective performance and ease of use, the majority of the patients preferred the suspension with the pressurized ampoule. Therefore it would appear to us that the above therapy in the present dosage does produce short-term improvement in ventilatory capacity but not more than might be expected by isoprenaline alone. There is nothing in the present evidence to suggest that chymotrypsin in the above dosage will facilitate the expectoration of sputum. There is evidence that chymotrypsin is apt to produce both allergic reactions and also non-specific laryngotracheitis.

## Summary

Thirty-five male patients were admitted to a chemotherapy trial using chymotrypsin and isoprenaline sulphate presented as a fine dry powder or suspended in an inert propellant.

The indices of assessment were sputum weight and F.E.V.$_1$.

Sequential analysis indicated no therapeutic difference between the powder and the suspension.

There was no evidence that the weight of the sputum in the therapy period was different from that in the control period.

The F.E.V.$_1$ was significantly increased at three minutes after both therapies. At six hours there was a reduction of the F.E.V.$_1$ below that of the control period which was not statistically significant.

Five patients had to discontinue therapy subsequently on account of allergic reactions. One patient discontinued therapy on account of severe non-specific laryngotracheitis.

We are indebted to Mrs. D. Weightman for help with the statistical calculations. We thank Riker Laboratories Ltd. for a generous supply of "medihaler" units containing chymotrypsin and isoprenaline.

### REFERENCES

Armitage, P. (1957). *Biometrika*, **44**, 9.
Fullgrabe, E. A. (1957). *Ann. N.Y. Acad. Sci.*, **68**, 192.
Lichtman, A. L. (1957). Ibid., **68**, 196.
Liebowitz, D., and Ritter, H. (1960). *J. Amer. med. Ass.*, **172**, 159.
Maclaren, W. R., and Aladjem, F. (1957). *J. Allergy*, **28**, 89.
Robinson, W., Woolley, P. B., and Altounyan, R. E. C. (1958a). *Lancet*, **2**, 821.
—— —— —— (1958b). Ibid., **2**, 819.

The Chadwick Medal for the best postgraduate student in public health engineering at Durham University Department of Civil Engineering was presented to Mr. ERIC P. MUNRO, executive officer, Housing and Town Planning Authority, Dominica, B.W.I., by Sir SELWYN SELWYN-CLARKE, at King's College, Newcastle upon Tyne, on June 16.

# CRYPTOCOCCAL MENINGO-ENCEPHALITIS

BY

W. F. TWINING McMATH, M.D., M.R.C.P. D.P.H.

*Physician Superintendent, Neasden Hospital, London*

AND

K. K. HUSSAIN, M.D.

*Assistant Physician, Neasden Hospital, London*

Busse (1894, 1895, 1896) and Buschke (1895) reported the presence of yeast-like organisms in a 31-year-old woman with a "gumma-like" or sarcoma-like affection of the tibia. She also had lymphadenopathy and secondary skin lesions followed by involvement of the knee-joint; after death multiple lesions in the bones, skin, lungs, spleen, and kidney were found. Vuillemin (1901) differentiated this organism from the true yeasts and named it *Cryptococcus hominis*. Versé (1914) reported what was believed to be the first human case of cryptococcosis of the nervous system diagnosed before death. He recorded an extensive leptomeningitis in a woman of 29 years.

The consensus of opinion of medical mycologists is that the most suitable name for the pathogen is *Cryptococcus neoformans*. *C. neoformans* is the organism most often present in mycotic meningitis cases in man. It is found in milk and milk products, in fruit, on the skin, and in the mouth. The disease is thought to be rare; most cases are reported from America and Africa. The recorded cases do not represent the true incidence, for many have been misdiagnosed as lymphocytic, tuberculous, or syphilitic meningitis.

Because of the infrequency with which these cases are reported and the greater use of antibiotics, which is likely to increase the incidence of fungal diseases, the following case is put on record.

## Case Report

The patient, a boy aged 4 years, was born of West African parents. His mother, a qualified nurse, had him immunized against all the common conditions, including poliomyelitis and tuberculosis. In March, 1960, she noticed a rash on his face which she thought was a fungal infection, and treated it with local applications of nystatin.

On September 1 he had a fall and sustained a head injury. That evening he complained of frontal headache and vomited. Subsequently he remained well until September 7, when there was a recurrence of frontal headache and vomiting, and he had vague abdominal pain. This persisted until September 10 and culminated in a convulsion, followed by pyrexia.

On admission to a general hospital his temperature was 100° F. (37.8° C.), but no localizing signs in the central nervous system, apart from abnormal irritability. A tentative diagnosis of subdural haematoma was made and he was kept under observation. Investigations showed: E.S.R., 15 mm./1st hour (Wintrobe); Hb, 12.1 g./100 ml. (82%); W.B.C., 14,100 (P.74%, L.21%, M.5%); Mantoux test 1/1,000 was negative in spite of B.C.G. inoculation.

By September 12 he had marked signs of meningeal irritation, screaming episodes, and continued pyrexia. A lumbar puncture produced fluid at normal pressure which contained R.B.C. 42/c.mm., W.B.C. 64/c.mm. (all lymphocytes), protein 10 mg./100 ml., sugar 84 mg./100 ml., and chlorides 680 mg./100 ml. Next day his symptoms became worse. Examination of the fundi revealed nothing abnormal. Lumbar puncture was repeated, the findings being: R.B.C. 635/c.mm, W.B.C. 112/c.mm. (all lymphocytes, protein 10 mg./100 ml., sugar 75 mg./100 ml. At this stage a diagnosis of "non-specific lymphocytic meningitis" was made and he was treated symptomatically. Virological studies were undertaken, with negative results.

On September 14 his speech became slurred. He was drowsy and incontinent of urine. Generalized muscular weakness and flaccidity of limbs developed. The fundi remained normal, but pupillary reaction to light became very sluggish, and there was well-marked ptosis of the left eye. He then developed difficulty in swallowing, with accumulation of saliva in the throat. Meningo-encephalitis with bulbar palsy was suspected, and as his condition continued to deteriorate steroid therapy was begun. On September 15 he was transferred to Neasden Hospital, the regional centre that dealt with bulbar palsies.

On examination at Neasden Hospital the patient was found to be fully conscious but irritable. The skin was clear, his rectal temperature 98.6° F. (37° C.), and his throat intensely congested, with enlarged tonsils showing a fair amount of exudate. He asked for ice-cream, which was immediately offered to him. He swallowed quite well, and as he had gained confidence examination of the central nervous system was not difficult. The fundi were normal; there was marked ptosis of the left eye; the left pupil was much larger than the right and its reaction to light was impaired; and conjugate eye movements were normal. The

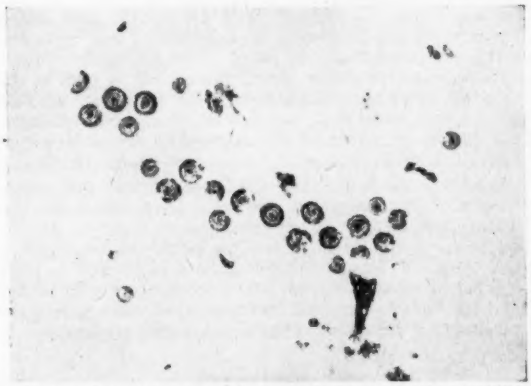


FIG. 1.—Photomicrograph of a nigrosin film, showing budding cryptococci.

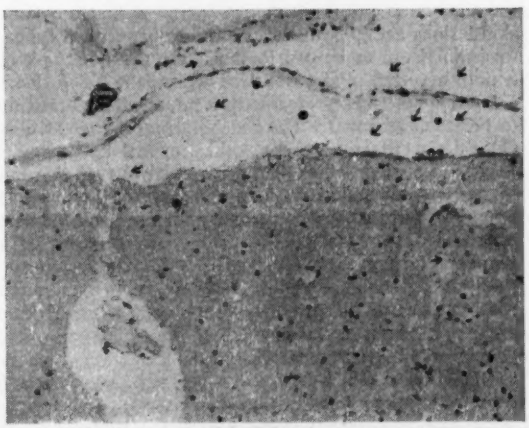


FIG. 2.—Photomicrograph of a section of cortex. Arrows point to capsulated spheroidal cryptococci.

palate moved well on phonation, and his speech, though slow, had no nasal element. All sensations seemed normal, but he had a complete areflexia. Although there was generalized flaccidity of limbs, voluntary movements were possible. The diaphragm and intercostal muscles acted well. There were no other physical signs of any significance.

The chest *x*-ray picture was within normal limits. Hb was 9.9 g./100 ml. (67%); the blood group B, rhesus-positive; and there was no evidence of sickle-cell trait. Urine showed a trace of albumin only, porphyrins were not detected. Throat culture did not grow *Corynebacterium diphtheriae* or haemolytic streptococci. A direct smear from the throat was negative for organisms of Vincent's angina, candida, and yeast cells. A lumbar puncture was not performed immediately as he had had one so recently.

His condition remained unchanged until September 17, when he gradually lapsed into coma—that is, about 36 hours after admission. At this stage a lumbar puncture yielded a slightly turbid fluid that was at first reported to contain R.B.C. 88/c.mm., lymphocytes 72/c.mm., and 322 other cells per c.mm., which were thought to be "endothelial cells." All other constituents of the cerebrospinal fluid were normal. This sounded very suspicious, and on request a smear was made and stained with indian ink. This revealed that the so-called "endothelial cells" were in fact cryptococci (later identified as *C. neoformans* by the London School of Hygiene and Tropical Medicine). A photomicrograph of a nigrosin film is shown (Fig. 1).

*Treatment.*—Until the diagnosis was made the child was treated symptomatically. Steroid therapy had started before admission. He had two 5-mg. doses of prednisolone while under our care, and tetracycline 250 mg. six-hourly. At first he was taking "complan" well by mouth, with added vitamins. When he became drowsy, feeding was continued via a plastic naso-gastric tube. Thus his water-and-salt balance was kept within normal limits, and, as soon as the diagnosis was made, specific therapy was instituted. He was given amphotericin B, 0.5 mg. in 5 ml. of water intrathecally, and 20 mg. in 250 ml. of 5% dextrose by intravenous drip. Unfortunately he died on the evening of September 17.

*Necropsy Findings.*—The C.S.F. was turbid, and, apart from a slight oedema of the brain tissue, there was no macroscopic evidence of any inflammatory reaction. Microscopically there was slight swelling of the pia-arachnoid, a few scattered leucocytes and plasma cells, but a large number of capsulated spheroidal cryptococci (Fig. 2). Other findings were a terminal bronchopneumonia, early pericarditis, and peritonitis. The suprarenals were healthy.

## Discussion

Fungal infections are perhaps more common since the introduction of antibiotics. Unless blastomycotic skin lesions are present the possibility of visceral fungal invasion is apt to be overlooked. We did not think of it until a verbal report was received on the C.S.F. from a lumbar puncture performed 36 hours after admission to Neasden Hospital. The fact that protein, sugar, and chlorides were found to be within normal limits points to an inherent inability of the cryptococcus to give rise to any immediate acute inflammatory reaction. This apparent failure of the primary defence mechanism appears to be associated with low antigenicity of a number of fungi. Cryptococci may invade tissues and multiply by budding without giving rise to an inflammatory reaction, because they do not seem to produce an exotoxin. After a varying length of time their mere presence in larger numbers comes to be regarded as foreign bodies which lead to an infiltration with round cells and macrophages (usually with giant-cell formation), and so a granulomatous lesion is produced. In cryptococcal meningo-encephalitis, granulomata are usually found at the base of the brain, but these were not present in our patient. Therefore the spinal fluid is not likely to show much alteration other than a marked pleocytosis, as in our case, and consequently the diagnosis depends on the detection of the yeast-like cells.

There are conflicting reports that complement-fixing antibodies are present in the serum of patients suffering from cryptococcosis. Neill *et al.* (1949, 1951) claim to have demonstrated precipitins in the spinal fluid, urine, and blood of patients, and a specific capsular reaction in immune rabbit serum. Diagnostic hypersensitivity skin tests have also been described, but are unreliable (Evans and Theriault, 1953).

It will be recalled that there was a vague history of fungal infection of the face which was treated locally with nystatin. It is possible that this may have been the site of the original infection, and presumably dissemination was either embolic or through the respiratory or the intestinal tract. Approximately 80–90% of patients with cryptococcal meningo-encephalitis die within the first year, many within six months, of the onset of neurological manifestations (Littman and Zimmerman, 1956). Some, however, live a considerable time in spite of the presence of viable cryptococci in the C.S.F.

In assessing the efficacy of new fungicidal drugs, the fact that natural remissions occur must be remembered, and these necessitate a prolonged period of observation. Many antibiotics and other drugs have been used without great success, including streptothricin and actidione. Recently amphotericin B ("fungizone") has given more encouraging results, especially when the nervous system is not involved. Martin *et al.* (1959) described five cases of cryptococcal meningo-encephalitis which were given 50–100 mg. of the drug dissolved in 250–500 ml. of 5% dextrose solution intravenously daily for six weeks. In three cases the condition appeared to be arrested, but relapse occurred in the remaining two. Pimstone and Saunders (1959) note that intrathecal administration of the drug in a dose of 0.5–1 mg. in 5 ml. of distilled water may be used when the central nervous system is involved, and is said to produce a C.S.F. fungicidal level for 24–48 hours.

## Summary

A case of cryptococcal meningo-encephalitis with post-mortem findings is described.

The known low antigenicity of *Cryptococcus neoformans* is correlated to the pathological findings—namely (*a*) in the central nervous system there were only a few scattered leucocytes and plasma cells in spite of the presence of a large number of cryptococci; and (*b*) during life the cerebrospinal fluid showed red blood cells, lymphocytes, and cryptococci, but protein, sugar, and chlorides were normal. This suggests a host-parasite armed neutrality with unpredictable dissemination at any time.

Ultimate prognosis seems to be uniformly bad, and one must admit that, at present, specific treatment is far from satisfactory.

We are indebted to Dr. D. A. D. Bowen, of St. George's Hospital Medical School, who carried out the post-mortem examination, for the microscopical section of the nervous system; to Dr. D. R. Gamble, of Neasden Laboratory, for the slide upon which the diagnosis was made; and to Mr. A. G. Booker, of the photographic department of the Central Middlesex Hospital for the photomicrographs.

REFERENCES

Busse, O. (1894). *Zbf. Bakt.* **16**, 175.
—— (1895). *Virchows Arch. path. Anat.*, **140**, 23.
—— (1896). Ibid., **144**, 360.
Buschke, A. (1895). *Dtsch. med. Wschr.*, **21**, 14.
Evans, E. E., and Theriault, R. J. (1953). *J. Bact.*, **65**, 571.
Littman, M. L., and Zimmerman, L. E. (1956). *Cryptococcosis*, p. 121. Grune & Stratton, New York and London.
Martin, W. J., Nichols, D. R., Svien, H. J., and Ulrich, J. A. (1959). *Arch. intern Med.*, **104**, 4.
Neill, J. M., Castillo, C. G., Smith, R. H., and Kapros, C. E. (1949). *J. exp. Med.*, **89**, 93.
—— Sugg, J. Y., and McCauley, D. W. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **77**, 775.
Pimstone, B. L., and Saunders, S. J. (1959). *S. Afr. J. Lab. clin. Med.*, **5**, 156.
Versé, M. (1914). *Verh. dtsch. path. Ges.*, **17**, 275.
Vuillemin, P. (1901). *Rev. gen. Sci. pûres appliq.* **12**, 732.

# RAPID SELECTION OF GROUP A RECIPIENTS AMONG MASS CASUALTIES

BY

**P. D. STEWART, M.D., D.T.M.&H.**

*Consultant Pathologist, Vale of Leven Hospital, Alexandria, Dunbartonshire; Major, R.A.M.C.(T.A.)*

One of the major advances in medicine in the 1939–45 war was the development of an efficient blood transfusion service which was able to provide an adequate supply of group O blood for the emergency treatment of casualties. In the event of another major conflict, the use of atomic and nuclear weapons is likely to result in much heavier civilian and military casualties with consequently a much increased demand for blood.

The use of suitable group O blood only for the emergency transfusion of casualties has one great advantage—namely, that the blood can be given without knowledge of the patient's blood group and without prior cross-matching. In the 1939–45 war disasters from incompatible blood transfusion were almost unknown (Whitby, 1953), and in Korea most of the recorded transfusion reactions followed the use of locally procured blood instead of the doubly checked group O blood which was normally supplied (Crosby, 1955). A major criticism of restricting blood used for casualties to group O only is that it results in an unbalanced utilization of the donor panel; for, in the United Kingdom, only some 47% of the population belong to group O and 42% are group A, 8% group B, and 3% group AB (Dobson and Ikin, 1946).

From the distribution of the ABO groups, it can be seen that if group A blood could be used, it would be possible nearly to double the supply of blood available for the emergency treatment of mass casualties. The essential requirement for such a scheme is a rapid yet reliable method of distinguishing group A and AB casualties, who could receive group A blood (A recipients), from group O and B casualties, who would still require group O blood (O recipients).

Zeitlin (1954) described a method of selecting group A recipients by a simple test which consisted of adding one drop of tap-water and one drop of patient's blood to a slide coated with potent anti-A serum and watching for microscopic agglutination, which occurred within one minute with groups A and AB. For urgent cases, especially obstetrical emergencies, Zeitlin suggested the use of O and A rhesus-negative blood for O and A recipients respectively. He also suggested that the method of dividing emergency cases into two major groups according to the reaction obtained with a single test serum had an obvious practical application in large-scale emergency work—for example, in dealing with civilian or military casualties, rail accidents, and the like. Akeroyd and Crosby (1955) have discussed the advantages of using Zeitlin's method to increase the supply of blood in the event of war or a major disaster.

This paper describes three trials which were carried out to test the feasibility of rapidly selecting A recipients under field conditions. Similar trials have been conducted by J. H. Akeroyd (1958, personal communication) in America, and by H. C. Jeffrey (1960, personal communication) with British troops in Germany.

## The Trials

*Trials 1 and 2.*—These trials were carried out in 1957 with the co-operation of a field ambulance which organized two night exercises involving the admission and documentation of "casualties" at the rate of approximately one a minute. Blackout conditions were observed. The reception tent was lit by pressure lamps and hurricane lamps only. Blood-grouping was carried out by two teams, each consisting of two laboratory technicians with considerable experience in blood-grouping. Blood was obtained from each "casualty" by finger-prick. One drop was placed on a Zeitlin slide together with one drop of water and the slide examined for agglutination after one minute. In addition, a few drops of blood were added to a tube containing normal saline. The cell suspensions were ABO blood-grouped next day in the laboratory by the tube method.

In the first trial the personnel reading the slide tests often experienced difficulty in deciding whether or not agglutination was present, and this difficulty was greatest in those parts of the reception tent where the lighting was poorest. For the second trial electric head-lamps were used; these gave satisfactory illumination, making agglutination, if present, obvious.

*Trial 3.*—This was carried out in 1960 at a Territorial Army training camp. On this occasion liquid anti-A serum was used. Fingers were swabbed with iodine in 70% alcohol and a separate sterile disposable needle ("seralet") was used for each individual. A drop of blood was collected on to a clean slide and one drop of anti-A serum added. The blood and serum were mixed by means of the disposable needle and the slide was examined for agglutination after one minute. An electric head-lamp was used for illumination when the tests were carried out after dark. At the same time a few drops of blood were collected into glucose–citrate solution. The slide groupings were performed by day and by night under a variety of conditions—that is, in tents, huts, vehicles, and in the open. The first few tests were read by me, but most were carried out by a nursing orderly and an infantry private soldier, neither of whom had had any previous experience in blood-grouping. The only instruction these two men received was a short explanation at the beginning of the trial and a demonstration on the first few groupings carried out. The cell suspensions were forwarded to the East of

Scotland Blood Transfusion Service, Dundee, where the ABO groups of the cells were determined under laboratory conditions.

### Results

The results of the slide agglutinations and of the grouping of the cell suspensions in the laboratory are compared in the accompanying Table.

The errors in the reading of the slide tests have been divided into two categories: (1) major errors which would result in an incompatible transfusion—that is, reading agglutination where none should have been present and

*Comparison of Slide Test with Laboratory Grouping*

| Trial | Total | Agreement | Major Errors | Minor Errors |
|---|---|---|---|---|
| 1 | 84 | 72 | 10 | 2 |
| 2 | 100 | 96 | 1 | 3 |
| 3 | 178 | 178 | — | — |
| Total | 362 | 346 | 11 | 5 |

thereby labelling an O or B patient as an A recipient; and (2) minor errors not likely to prejudice the safety of a transfusion—that is, where agglutination was missed and an A or AB patient was labelled as an O recipient.

### Discussion

It is considered that most of the major errors in the first trial were due to difficulty in reading agglutination under unsatisfactory lighting conditions and to faulty planning and recording of results. This opinion is supported by the results of the second and third trials, where electric torches were used and where the recording of results and the labelling of the control samples were more satisfactory. No technical explanation can be offered for the one major error in the second trial, and it is assumed that it must have been the result of a clerical mistake.

It would appear, from these trials, that, provided certain simple precautions are taken, distinguishing between group O and A recipients under field conditions by the use of a slide agglutination, using anti-A serum, is a practical proposition. If we exclude the first trial, where the methods, especially the illumination, were unsatisfactory, we find that the serious error in 278 tests was 0.3%. The method is therefore not free from risk, but it is possible to imagine circumstances where it would be justifiable to take this risk in order to increase the amount of blood available. The technique is simple and can be learned quickly by an intelligent person with no previous laboratory experience.

If this scheme were to be used in circumstances where casualties might include females, it would be important to incorporate a proportion of rhesus-negative blood in the supplies of groups O and A blood allotted for the emergency treatment of the injured.

There would appear to be little advantage and an obvious disadvantage in expanding the scheme to include the use of B and AB blood. Approximately 11% of the population belong to groups A and AB, and the inclusion of these groups would necessitate more elaborate blood-grouping procedures, with an increased risk of error without any great resulting increase in the amount of blood available. If, however, such a step were contemplated hen grouping by Eldon (1955) card might prove to be the method of choice.

It would be possible to dispense with any form of testing when selecting A recipients in the case of casualties who carried reliable documentary evidence—that is, a National Blood Transfusion Service donor card showing their blood group, although the slide test with anti-A serum could still be used as a check before transfusion.

The method of selecting A recipients by the use of anti-A serum alone, first suggested by Zeitlin (1954), is an emergency procedure designed to conserve blood supplies and one to be used only in circumstances where full blood-grouping and cross-matching cannot be performed.

### Summary

The supplies of blood available for the emergency treatment of mass casualties, either civilian or military, could be almost doubled if group A blood as well as group O blood were to be used.

A simple method of selecting group A recipients has been tested under field conditions. When used under these conditions it carries a slight but probably justifiable risk.

I am indebted to Lieutenant-Colonels E. G. Wright and A. D. R. G. Wilson for their willing co-operation, to Dr. R. A. Zeitlin for a supply of coated slides, to Dr. C. Cameron for his help with the third trial, to Dr. J. Wallace for the supply of liquid anti-A serum, and to the various laboratory technicians and Private McCormack for their assistance.

#### REFERENCES

Akeroyd, J. H., and Crosby, W. H. (1955). *J. Amer. med. Ass.*, **159**, 424.
Crosby, W. H. (1955). *Milit. Med.*, **117**, 354.
Dobson, A. M., and Ikin, E. W. (1946). *J. Path. Bact.*, **58**, 221.
Eldon, K. (1955). *Dan. med. Bull.*, **2**, 33.
Whitby, L. E. H. (1953). In *History of the Second World War, United Kingdom Medical Series. Surgery*, edited by Z. Cope, p. 46. H.M.S.O., London.
Zeitlin, R. A. (1954). *Lancet*, **1**, 23.

# Preliminary Communications

## Small Doses of Intra-arterial $^{32}P$ in Location of Cerebral Tumours for Biopsy

The ability of cerebral tumours to take up radioactive salts or protein to a greater extent than normal brain has been known for some years. One use of this property has been the locating of tumours at operation or biopsy after intravenous injection of an active isotope of phosphorus, using a probe-pattern geiger-counter to explore the brain at operation. The recommended dose of isotope for intravenous injection in such a study has been variously given as 1 millicurie (Morley and Jefferson, 1952), 0.5 to 1 $\mu$c (Selverstone and White, 1951), or "1 $\mu$c or less" (Selverstone and Moulton, 1957).

In the course of blood-flow studies in the cerebral cortex, using smaller quantities of isotope by intra-arterial injection, a differential count, adequate for location, was obtained in a number of tumours. This small series annotates the study of 12 space-occupying lesions after the administration of 50 $\mu$c of $^{32}P$ into the common carotid artery, undertaken to discover whether such a small dose of isotope could give consistently reliable results.

*Method.*—The cases had been fully investigated as in-patients, and the site and supratentorial situation of the space-occupying lesion was already established. Under general anaesthesia 50 $\mu$c of $^{32}P$ (as carrier-free solution in 0.005 ml. of HCl) in 10 ml. of saline was injected into the appropriate common carotid artery. In most cases carotid angiography had already been performed, but in all cases a low puncture was made in the neck to diminish the possibility of external carotid injection. A trephine disk or bone flap was then raised and the probe study performed at an interval after isotope injection varying from 30 to 90 minutes. The probe used was a 3-mm. type N 1 b (20th Century Electronics). Counts were passed to a rate-meter and displayed on a pen-recorder.

## RESULTS

The site and nature of the 12 cases studied by this method are given in the Table. In the two non-tumour cases the clinical diagnosis, after angiography and ventriculography, lay between an intracerebral haematoma and a cystic glioblastoma.

The differential count between tumour and brain followed the pattern described by other investigators in that the highest contrast occurred with secondary tumours (Fig. 1), meningiomas (Fig. 2), or anaplastic glioblastomas (Fig. 3). The poorest contrast, and the greatest difficulty in diagnosis, occurred in the low-grade astrocytomas—an example is shown in Fig. 4. Record "a" was obtained from uninvolved cortex in the frontal region. Record "b" was obtained from the white matter of the temporal lobe, which, after lobectomy, was confirmed as being scantily infiltrated by protoplasmic astrocytoma (grade I). In "c" is shown the record obtained with the counter in the medial part of the temporal lobe in the region of the uncus. After lobectomy this area was found to have the histological character of a gemistocytic astrocytoma (grade II). The count-rate is much higher than in the less cellular area of the tumour. Both the non-tumour cases studied presented a large, relatively smooth-walled cyst. In one, symptoms had been present for 12 months, with ictal deterioration four weeks before the probe study was made. No increase in uptake of $^{32}P$ was detectable in the wall of the cyst in this case. In the other case, where symptoms had been present for only 10 days before the probe study, there was a greatly increased uptake of $^{32}P$ in the cyst wall as compared with normal neighbouring white matter (Fig. 5). Histological examination of the cyst wall showed vascular granulation tissue with numerous reacting astrocytes, but no evidence of tumour.

## DISCUSSION

The use of a dose of 50 $\mu$c by intra-arterial injection—that is, one-tenth to one-twentieth of the dose suggested for intravenous use—avoids the necessity for isolation of the patient or special methods of disposal of the urine. It also accords with the present trend severely to restrict the dose of radioactive isotope in purely investigative procedures, and greatly reduces the difficulty of handling the isotope in a neurosurgical unit where such material is used only occasionally. In the first 48 hours after injection it is wise to have a catheter *in situ*, particularly if there is a risk of incontinence, but the urine may be disposed of in the usual way.

Adequate uptake for tumour location is obtained only within the field of supply of the injected artery. In the cases described, only the carotid field has been injected, as for practical purposes this includes the majority of tumours in which an operative probe study by any method is of use.

Bender (1959), using a gamma-emitting isotope by intravenous injection, suggested that for some weeks after cerebral angiography uninterpretable increases in activity in the hemisphere injected by contrast medium occurred. In the present small study there was no evidence that alteration in the pattern of uptake of $^{32}P$ occurred soon after carotid angiography.

*Location and Pathological Nature of Cases Studied*

| Case No. | Site | Histological Diagnosis |
|---|---|---|
| 1 | Right superior parietal | Reticulum-cell sarcoma ? metastatic |
| 2 | Septum pellucidum and head of right caudate nucleus | Glioblastoma |
| 3 | Right temporo-parietal | Intracerebral haematoma |
| 4 | Right temporal | Astrocytoma grade I–II |
| 5 | Left parietal | Glioblastoma |
| 6 | Right " | " |
| 7 | Left frontal | Meningioma |
| 8 | Right fronto-temporo-parietal | Astrocytoma grade II |
| 9 | Left post-temporal | Metastatic adenocarcinoma |
| 10 | Right fronto-parietal | Astrocytoma grade I |
| 11 | Left mid-parietal | Intracerebral haematoma |
| 12 | Left parietal parasagittal | Meningeal fibrosarcoma |

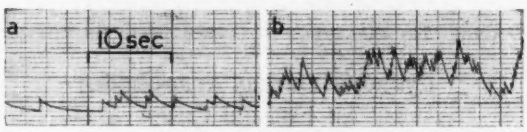



FIG. 1.—Case 9. Count-rates obtained from normal cortex (*a*) and from tumour (*b*).

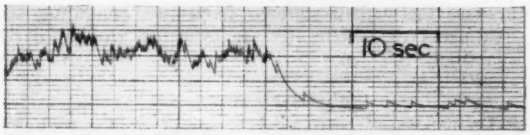



FIG. 2.—Case 7. Change in count-rate obtained as the counter was advanced from tumour at left of figure into normal brain at right.

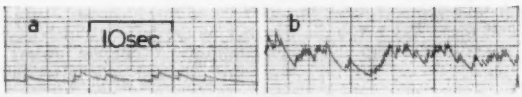



FIG. 3.—Case 5. Count-rates obtained from normal cortex (*a*) and from tumour (*b*).

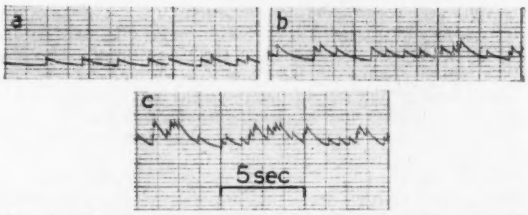



FIG. 4.—Case 4. Count-rates obtained from normal cortex (*a*) and from two areas of astrocytoma of differing cellularity (*b* and *c*).

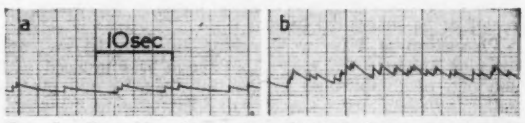



FIG. 5.—Case 11. Count rates obtained from normal white matter (*a*) and from the wall of a recent intracerebral haematoma (*b*).

SUMMARY

Brain tumours have been successfully located by probe-counting after the intra-arterial injection of 50 $\mu$c of $^{32}P$.

The pattern of uptake of various tumours has been the same by this method as after intravenous injection of isotope.

The inconveniences of handling the larger quantities of $^{32}P$ necessary for intravenous use are reduced.

I thank Sir Charles Harington, F.R.S., for facilities provided in the National Institute for Medical Research, and Mr. Valentine Logue for permission to study cases under his care.

LINDSAY SYMON, F.R.C.S., F.R.C.S.Ed.,
Clinical Research Fellow, M.R.C.
From the National Institute for Medical Research, Mill Hill, London, and Maida Vale Hospital for Nervous Diseases, London.

REFERENCES

Bender, M. A. (1959). In *Medical Radioisotope Scanning*, p. 207. International Atomic Energy Agency, Vienna.
Morley, J. P., and Jefferson, G. (1952). *Brit. med. J.*, **2**, 575.
Selverstone, B., and Moulton, M. J. (1957). *Brain*, **80**, 362.
—— and White, J. C. (1951). *Ann. Surg.*, **134**, 387.

# Medical Memoranda

## Cyanosis During Anaesthesia: An Unusual Case

The following case is described because of the unusual cause of cyanosis occurring during anaesthesia and because the patient suffered from two conditions the treatments of which are apt to cause trouble if an anaesthetic is given.

CASE REPORT

The patient, a woman aged 40, was admitted to a surgical ward for repair of an incisional hernia after hysterectomy. She was a thin pale woman with marked rheumatoid arthritis of both hands, elbows, and knees. No obvious cyanosis or jaundice was detected. Her blood-pressure was 210/110 and there was a systolic murmur at the left sternal border. There were some basal crepitations. Moderate anaemia (Hb, 9.16 g./100 ml.) was present and she also had symptoms of peptic ulceration, for which she had been in hospital four years before.

The patient suffered from a peptic ulcer, anaemia, hypertension, and rheumatoid arthritis, apart from the condition for which she was admitted. She took an alkaline mixture for the relief of the pain from the peptic ulcer. She had had various forms of treatment for rheumatoid arthritis but had never had steroid therapy. She was receiving treatment for anaemia and was having a preparation of reserpine for hypertension. Two days after admission she developed a temperature of 101° F. (38.3° C.) with "aches in her bones." Because of this and because she had been on hypotensive therapy the operation was postponed and the therapy stopped. She was given sodium phenobarbitone 30 mg. t.i.d. and was kept in bed. Five days later her blood-pressure was 150/90 and she was feeling quite well. After a further three days she was taken to the theatre for repair of her incisional hernia.

Premedication was by morphine sulphate 10 mg. and atropine sulphate 0.6 mg. Anaesthesia was induced with 300 mg. of thiopentone sodium followed by 120 mg. of gallamine triethiodide. A No. 10 cuffed endotracheal tube was passed and anaesthesia was maintained by nitrous oxide, oxygen, and 0.5% halothane, using a Fluotec vaporizer with a flow-rate of 3 litres of nitrous oxide and 1.5 litres of oxygen. Controlled respiration with carbon-dioxide absorption through a Waters absorber was used.

When the operation was started it was noticed that the blood was blue and the patient looked slightly cyanosed. Although oxygenation and ventilation appeared adequate the concentration of oxygen was increased and the tidal volume raised. This did not produce any improvement. Auscultation of the chest revealed equal and adequate inflation of the lungs and no abnormality could be detected in the heart action. The systolic blood-pressure was about 130 mm. Hg.

As I had previously heard of two cases of sulphaemoglobinaemia during anaesthesia and had recently discussed these cases with others I thought that the patient might also have sulphaemoglobinaemia. Accordingly blood was withdrawn and sent for spectroscopic examination. The report, which was obtained within minutes, stated: "Sulphaemoglobin was detected and was visible in dilution up to 1:40" (Dr. R. G. S. Leask).

The operation and anaesthesia thereafter continued uneventfully although cyanosis persisted. On questioning the patient later she said that she had been accustomed to taking large amounts of a proprietary analgesic containing phenacetin.

COMMENT

This patient had two conditions, rheumatoid arthritis and hypertension, the treatments of which are known to cause so-called iatrogenic disease which can complicate anaesthesia (Dundee, 1958). She managed, however, to avoid both these pitfalls, but instead complicated the anaesthesia by self-medication. By taking a proprietary analgesic containing phenacetin she developed sulphaemoglobinaemia, producing cyanosis, which, though not detected pre-operatively, became obvious during anaesthesia.

I thank Mr. W. Gray, surgeon, and Dr. R. G. S. Leask, biochemist, for their co-operation.

W. SNIPER, M.B., Ch.B., F.F.A. R.C.S.,
Consultant Anaesthetist,
Stobhill General Hospital, Glasgow.

REFERENCE

Dundee, J. W. (1958). *Brit. med. J.*, **1**, 1433.

A Joint Expert Committee on Food Additives of the Food and Agriculture Organization and W.H.O. has been studying the amount of certain natural and synthetic additive compounds that can be consumed daily without harmful effects. Earlier meetings of this joint committee, concerned with more general aspects of the problem, had stressed the need for an evaluation of the toxicological risks in the use of food additives. They recommended that a beginning be made on assessing the biological properties of a number of substances used as antimicrobials and antioxidants which are widely used to prevent wastage, especially in tropical countries where heat destroys the keeping qualities of many foods. The present meeting of the committee prepared a monograph on each of the 35 antimicrobials and antioxidants under review. These monographs will probably be published in the W.H.O. Technical Report Series and should prove to be especially useful in the developing countries to help officials and technicians who are framing laws and regulations for the protection of the public. Throughout the eight days of the discussions it was constantly stated that each country would ultimately have to find its own solution to the problem of any particular food additive, because conditions of life, food habits, and dietary patterns vary so greatly. The committee believed, however, that baby foods should be prepared without food additives at all, if possible.

# Reviews

## ANATOMY OF THE MACHINE

*The Art of Administration.* By A. Leslie Banks, M.A., M.D., F.R.C.P., D.P.H., and J. A. Hislop, M.A., M.D., F.R.C.P.(Edin.). (Pp. 224. 12s. 6d.) London: University Tutorial Press Ltd. 1961.

Good administration is essential to any advanced society in modern conditions; without it wise policy, good plans, and generous intentions go sadly awry. As Ernest Bevin once remarked, "Bleeding 'earts are no use; what we need is bloody brains." Not many years ago the Cabinet could govern this country without a secretariat and its members might have little knowledge of the administrative problems arising from their decisions. The stress and complexity of business in war, however, and the increasing penetration of central and local government into the affairs of private citizens put an end to the old informal system and led to the enormous expansion of administrative bureaucracy that so alarmed Lord Hewart in 1932. In commerce the chief economic consequence of power production was the integration of capital resources and the formation of vast enterprises with world-wide connexions; no longer could the boss dispose of all administrative problems as he could when he made his daily round of the works and knew most of his employees by their Christian names. Administrative machinery became clearly necessary, and this book is directed at all those who come into contact with the machine for the first time. It is in two parts: the first, rather like a textbook of topographical anatomy, describes the different parts of the whole machine—Parliament, central and local government, the civil service, the judiciary, voluntary and public bodies, with separate chapters on university administration and financial control. The second part is distilled from the combined experience of the authors, who claim to have served in nearly every type of administration during the past 35 years. In so doing they should at least have escaped monotony and be qualified to express opinions on the all-important matter of personal relationships between those who have to deal responsibly with their fellows.

The most interesting new growth in administrative machinery in this century has been the development of public corporations. Among these are the Central Electricity Board (1926), the B.B.C. (1927), the London Passenger Transport Board (1933), and the B.O.A.C. (1939). Nothing like them had existed in England previously. Their relations with Ministers and Parliament are ill-defined; some financial control remains with Parliament in respect of disposal of profits, the provision of loans, the right to obtain detailed information, and the institution of public inquiries. It will be interesting to see whether this system yields better results than complete nationalization.

The government of universities and hospitals in the National Health Service is exceptional. The University Grants Committee is a standing committee appointed by the Chancellor of the Exchequer to advise him on the financial needs of the universities and to prepare in consultation with them plans for their development. Considerable autonomy remains with the separate universities, but there is some apprehension that Treasury control may eventually inhibit academic freedom. So far this has not occurred and that happy result may be due to good administration. The hospitals are far more strictly controlled—and almost inevitably so. Their cost to the public purse is more than 10 times that of the universities. Regional boards and boards of governors are "agents" of the Minister, who selects their members after consultation with various interested bodies; they receive no remuneration, and it is remarkable that this country can still rely on so much voluntary service not only on the boards but on the hospital management committees and societies "of friends" On the whole the system has worked pretty well during the past 12 years. From time to time it has been suggested that the National Health Service might with advantage be transformed into a public corporation like the B.B.C. or the Central Electricity Board. One difficulty is that the Health Service is not a trade. It has no source of revenue other than the large subsidy from general taxation and the small sums collected by the sale of stamps and the charge for prescriptions. Whether or not it would be possible to make the Service partially self-supporting by instituting fees for consultations and treatment at home and in hospital is a proper subject for political discussion. That such a reform would be difficult to achieve and administer in England there is no doubt.

The only omission I noticed in this excellent monograph was the absence of any detailed discussion of the place of doctors in administration. There are statements on pages 190 and 191 that the medical man is by virtue of his training and experience ill-fitted for the work and that many clinicians dislike the medical administrator as a "power lover." Experience of the management of mental institutions and local authority hospitals did not make the office of medical superintendent generally popular, but there is no doubt that some of the superintendents were immensely successful in a difficult job in difficult conditions.

Good senior administrative medical officers of regional boards have shown recently how valuable previous professional experience may be in administration—at least they speak the same language and are inspired by the same ideals as the clinicians—and there is a case for reviewing the present policy in English hospitals.

A. P. THOMSON.

## FACTS AND FIGURES FOR HAEMATOLOGISTS

*Clinical Haematology.* By Robert Duncan Eastham, B.A. (Cantab.), M.D.(Cantab.), D.C.P., Dipl.Path. (Pp. 158. 15s. 6d.) Bristol: John Wright and Sons Ltd. 1961.

This book should be subtitled "Facts and Figures for Haematologists." It is a remarkable compilation of up-to-date quantitative information about haematology put together in a style reminiscent of Tidy's *Synopsis of Medicine.* It is divided into five sections: haemoglobins and associated pigments, red blood-cells, anaemia, peripheral white blood-cells, bone marrow, and lastly bleeding, clotting, and transfusion. Each section is divided up into many subsections and there are often a few references to the literature at the end of these subsections. In each of the subsections the significance of pathological variations is briefly discussed, and these discussions sometimes include useful explanatory notes—for example, on the blood volume changes in pregnancy. Good cross-references to allied sections are provided. There are some useful tables: for example, one on tests for identifying the various types of haemolytic anaemia, and one for distinguishing

the various clotting defects. Many unusual points and subjects are included: for example, plasma haptoglobin, red-cell enzymes and the glutathione-stability test, a long list of leukaemoid reactions and their causes, serum properdin, and the "Bridge" anticoagulant. In the anaemia sections, and in some other places, good *précis* accounts of present views on aetiology are included.

This is indeed very good value for money. Every clinical pathologist as well as every haematologist will find it useful for quick reference and refreshment of the memory.

M. C. G. ISRAËLS.

## VIRUS RESEARCH

*Advances in Virus Research.* Edited by Kenneth M. Smith and Max A. Lauffer. Volume 7. (Pp. 397+ix; illustrated. $10.) New York and London: Academic Press, Inc. 1960.

*Advances in Virus Research* first appeared in 1953 with a collection of articles on subjects of current interest in virology. The present volume, the seventh in the series, maintains the previous high standard, and the selection of subjects illustrates well the dramatic changes that have taken place in virology in recent times. Earlier studies on bacterial and plant viruses have opened up a way for the experimental study of animal and tumour viruses, their biosynthesis and structure. James B. Darnell and H. Eagle contribute a valuable chapter on the biosynthesis of poliovirus. The relationship between the viruses of measles, canine distemper, and rinderpest is discussed by Joel Warren in a comprehensive and up-to-date review. Sarah Stewart and Bernice Eddy each contribute a chapter on the S.E. polyoma virus of mice. In these chapters are to be found a mass of useful detail on the nature of the polyoma virus, methods of propagation, pathology of the tumours, and antigenic and physico-chemical properties. L. Kilham discusses the transformation of fibroma into myxoma virus and the behaviour of the D.N.A. of the two viruses concerned. New techniques for the study of the structure of small viruses are described and well illustrated by A. Klug and D. L. D. Caspar. The problem of non-specific resistance is discussed by A. A. Smorodintsev in a valuable review of this subject. Other chapters deal with variation in plant viruses and the biology of soil-borne plant viruses.

This edition, like the previous six, is extremely well produced, well set out with headings and subheadings at the beginning of each chapter, and with a comprehensive list of up-to-date references. This is a welcome addition to a valuable series on virus research.

J. A. DUDGEON.

## REVIEW OF PHARMACOLOGY

*Annual Review of Pharmacology.* Editor: Windsor C. Cutting. Volume 1. (Pp. 479+vii; illustrated. $7 in U.S.A., $7.50 elsewhere.) Palo Alto, California: Annual Reviews, Inc. 1961.

This is the first number of the *Annual Review of Pharmacology* and it contains several excellent reviews which will be most useful to pharmacologists. There are three chapters on highlights of Soviet pharmacology, Japanese pharmacology, and of Latin-American pharmacology. In Russia, as elsewhere, much attention is given to brain pharmacology. Attempts have been directed specially to the study of substances exerting a blocking action on central cholinergic synapses, and a series of substances have been recommended for clinical use. The first two which are mentioned are tropacin, described as the tropin ester of diphenylacetic HCl, and aprophen, the diethylaminoethylester of diphenylpropionic HCl. These substances antagonize the central action of anticholinesterases and of substances which act like acetylcholine. Further, centrally acting "cholinolytics" such as benactyzine prevent the formation of gastric ulcers induced by intense irritation of the duodenum. Thus benactyzine and related substances are held to have a central action which results in trophic effects. The Russians have also discovered new curare-like agents and new coronary dilators.

In Japanese pharmacology the action of haemolytic streptococci on tumour formation is being studied. Cell-free extracts of these streptococci have been prepared which have anti-cancer activity, attributed to an effect on the ribosenucleic acid of the tumour cell.

There is an excellent review by Erspamer on pharmacologically active substances of mammalian origin. He gives a critical appraisal of new work on histamine, hydroxytryptamine, angiotensin and renin, bradykinin, and other substances of this kind. This review would interest clinical workers as well as pharmacologists. Dews and Morse have written a chapter on the effect of drugs on behaviour which is not quite so difficult to read as such chapters usually are. Burns and Shore have contributed a useful article on the biochemical effects of drugs, and Trendelenburg has emphasized some interesting observations on transmission in autonomic ganglia.

The editors have chosen their authors very well. It may be hoped that they will ask the same authors to write again.

J. H. BURN.

## MANCHESTER FAMILY WELFARE CENTRE

*Family Welfare Centre.* By Nancy Lingard, Margaret Platt, M.B., Ch.B., D.P.M., and Barbara Oldham, M.B., Ch.B., M.R.C.S., L.R.C.P. (Pp. 44. 5s.) Available to social workers from the Family Welfare Centre, Darbishire House, Upper Brook Street, Manchester 13.

In 1944 Dr. Gertrude Jefferson, the wife of Professor Geoffrey Jefferson, approached the M.O.H. of Manchester, Dr. Metcalfe Brown, with a view to obtaining the co-operation of his council in setting up a new type of family welfare service. Her desire was to provide guidance in those problems which arose in family life, and which required rather more psychiatric advice and treatment than was then to be obtained through marriage guidance councils. Dr. Jefferson realized that, to deal adequately with many of these problems, some new and *ad hoc* clinic should be established. The Manchester Health Committee, though interested, was not at that time empowered to provide the necessary facilities. Action had therefore to be deferred until the broader powers of the National Health Service Act, 1946, were at its disposal and it became possible to provide both premises and a substantial grant. At a later date, this financial assistance was augmented by the generosity of the Nuffield Provincial Hospitals Trust.

This little volume recounts the various stages in the development of the family welfare centre, and describes the clinical material and the sources from which it came. Marital disharmony, manifesting itself often in the behavioural difficulties of the children, was at the root of a third of the cases which came to notice, and individual personal maladjustments, difficulties with

children, and cases of neurosis made up in equal proportion the greater part of the remainder.

This simple account of a pioneering project, entirely in keeping with the Manchester tradition, has been sympathetically written by Miss Lingard and Dr. Margaret Platt, who have been associated with the centre since its beginning. Dr. Barbara Oldham has added an account of a similar undertaking in Salford deriving from the Manchester experiment. Altogether it is a fitting tribute to the memory of Lady Jefferson.

J. A. CHARLES.

## DECADE OF FRACTURE TREATMENT

*Progress in the Treatment of Fractures and Dislocations, 1950–1960.* By Thomas B. Quigley, M.D., and Henry Banks, M.D. (Pp. 102. 17s. 6d.) Philadelphia and London: W. B. Saunders Company. 1960.

This excellent survey first appeared in the *New England Journal of Medicine*. It is a model of concise and informative writing and throughout is pleasantly readable. Being a critical review no illustrations are needed, nor are they given. There are, however, references to 426 articles in the literature—the vast majority from the English-speaking world. A significant new word is introduced: "most septic fractures are to some degree *chirurgenic* and contain plates, screws and rods." In the best sense, this little book is critical.

NORMAN CAPENER.

## BOOKS RECEIVED

*Review is not precluded by notice here of books recently received.*

***System of Ophthalmology.*** Volume II: ***The Anatomy of the Visual System.*** By Sir Stewart Duke-Elder, G.C.V.O., F.R.S., and Kenneth C. Wybar, B.Sc., M.D., Ch.M., F.R.C.S. (Pp. 901 + xxii; illustrated. £6 10s.) London: Henry Kimpton. 1961.

***Subnormal Personalities. Their Clinical Investigation and Assessment.*** By C. J. C. Earl, F.R.C.P.I., D.P.M., F.B.Ps.S. (Pp. 338 + xiv. 30s.) London: Baillière, Tindall and Cox. 1961.

***Handicapped Children.*** By John D. Kershaw, M.D., B.S., M.R.C.S., D.P.H. (Pp. 228 + x; 21s.) London: William Heinemann. 1961.

***A Short Manual of Venereal Diseases and Treponematosis.*** By R. C. L. Batchelor, M.A., M.B., Ch.B., D.P.H., F.R.C.S.Ed., F.R.C.P.Ed., and Marjorie Murrell, M.R.C.S., L.R.C.P., M.B., B.S., D.P.H., F.R.C.S.Ed. Second edition. (Pp. 316 + xvi; illustrated. 25s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

***Gynaecology for Senior Students of Nursing.*** By John Cairney, C.M.G., D.Sc., M.D., F.R.A.C.S. Second edition. (Pp. 225; illustrated. 30s.) Christchurch, New Zealand: N. M. Peryer Limited. 1961.

***Anatomy and Physiology for Nurses.*** By W. P. Gowland and John Cairney, C.M.G., D.Sc., M.D., F.R.A.C.S. Sixth edition. (Pp. 534; illustrated. 45s.) Christchurch, New Zealand: N. M. Peryer Limited. 1961.

***Common Nervous Disorders.*** By F. R. C. Casson, M.B., B.S., D.P.M. (Pp. 88. 4s.) London: W. and G. Foyle Ltd. 1961.

***The Adrenal Cortex. The Proceedings of a Symposium organized by the Association of Clinical Pathologists held in London at the Royal Society of Medicine, October 14th-15th, 1960.*** Edited by G. K. McGowan and M. Sandler. (Pp. 226 + xii; illustrated. 25s.) London: Pitman Medical Publishing Co. Ltd. 1961.

***Einfachheit und Sicherheit bei Magen- und Darmoperationen.*** By Dr. med. Heinrich Westhues. (Pp. 75 + viii; illustrated. DM. 29.) Stuttgart: Georg Thieme Verlag. 1961.

***Neuromuscular Disorders (The Motor Unit and Its Disorders).*** Proceedings of the Association for Research in Nervous and Mental Disease. Volume XXXVIII. Editors: Raymond D. Adams, M.D., Lee M. Eaton, M.D., and G. Milton Shy, M.D. (Pp. 813 + xx; illustrated. £8.) London: Baillière, Tindall and Cox. 1961.

***Modern Dietetics and the Vegetarian Diet.*** By K. Wilson James, M.R.C.P.(Edin.), F.R.C.S.(Edin.), F.I.C.S. (Pp. 40. No price.) London: K. W. Lewis. 1961.

***Bulletin de la Société de Chimie Biologique.*** Publié avec le Concours du Centre National de la Recherche Scientifique. By P. Malangeau, J. E. Courtois, and Y. Raoul. Volume XLII, No. 12. (Pp. 1,334–1,901 + viii; illustrated. NF. 55.) Paris: Masson et Cie. 1960.

***Pharmacodynamie Biochimique.*** Second edition. By Z. M. Bacq, J. Cheymol, M. J. Dallemagne, R. Hazard, J. La Barre, J. J. Reuse, and M. Welsch. (Pp. 1,227 + xvi; illustrated. NF. 140.) Paris: Masson et Cie. 1961.

***The Sounds of Language. An Inquiry into the Role of Genetic Factors in the Development of Sound Systems.*** By L. F. Brosnahan. (Pp. 250. 25s.) Cambridge: W. Heffer and Sons Ltd. 1961.

***Boletim Clinico e Estatistico.*** Hospital do Ultramar. (Pp. 281; illustrated. No price.) Lisbon: Grafica Santelmo. 1959.

***Progress in Biophysics and Biophysical Chemistry.*** Volume II. Editors: J. A. V. Butler, B. Katz, and R. E. Zirkle. (Pp. 277 + v; illustrated. 75s.) Oxford, London, New York, Paris: Pergamon Press. 1961.

***Newer Dimensions of Patient Care.*** Part I: ***The Use of the Physical and Social Environment of the General Hospital for Therapeutic Purposes.*** By Esther Lucile Brown, Ph.D. (Pp. 159. $2.) New York: Russell Sage Foundation. 1961.

***An Atlas of Juvenile MMPI Profiles.*** By Starke R. Hathaway and Elio D. Monachesi. (Pp. 402 + xviii. 64s.) Minneapolis: University of Minnesota Press. London: Oxford University Press. 1961.

***Report on Conference on Children with a Combined Visual and Auditory Handicap.*** Organized by the Rubella Group for Deaf/Blind Children at the Royal National Institute for the Blind, Condover Hall School, Condover, near Shrewsbury, Shropshire, on January 7 and 8, 1961. (Pp. 83; illustrated. 3s. 6d.) Published by the Group. 1961.

***Postoperative-Cataracte Spectacle Lenses.*** By Robert C. Welsh, M.D. (Pp. 123. $15:) Miami, Florida: The Miami Educational Press, Inc. 1961.

***Lehrbuch der Geburtshilfe.*** Revised by K. Klinke, F. v. Mikulicz-Radecki, B. Ottow, E. Philipp, L. Seitz, and W. Stoeckel. Edited by W. Stoeckel. Thirteenth revised edition. (Pp. 1,018 + xvi; illustrated. DM. 56.) Jena: Veb Gustav Fischer Verlag. 1961.

***Kombiniert abnorme Wesenzüge in neurotischen Reaktionen.*** By Bärbelies Bergmann. (Pp. 87. DM. 8.10.) Jena: Gustav Fischer Verlag. 1961.

***Exploración Clínica del Carazón. Orientaciones Actuales.*** By Dr. Pedro Zarco, in collaboration with Dr. Octavio Salmerón. (Pp. 173; illustrated. 210 ptas.) Madrid: Editorial Alhambra, S.A. 1961.

***Analysing Qualitative Data.*** By A. E. Maxwell, M.A., Ph.D. (Pp. 163. 16s.) London: Methuen and Co. Ltd. New York: John Wiley and Sons Inc. 1961.

***Bacteriology and Immunity for Nurses.*** By Ronald Hare, M.D. (Pp. 193 + viii; illustrated. 17s.) London: Longmans. 1961.

***I Servizi Sanitari a Bordo delle Grandi Navi.*** By Bruno Tertori-Donati. (Pp. 26; illustrated. No price.) Genoa: Istituto di Medicina del Lavoro dell'Università.

***The Extraction of Teeth.*** By Geoffrey L. Howe, M.R.C.S. (Eng.), L.R.C.P.(Lond.), F.D.S. R.C.S.(Eng.). (Pp. 70 + vi; illustrated. 17s. 6d.) Bristol: John Wright and Sons Ltd. 1961.

***Personality, and Success in Marriage.*** By Robert E. Morton. (Pp. 110. 10s.) London: William Heinemann. 1961.

***A Physician's Introduction to Electronics. A Laboratory Manual.*** By A. C. Morris, jun. (Pp. 43. 15s.) Oxford, London, New York, Paris: Pergamon Press. 1961.

***Physiology of the Salivary Glands.*** By A. S. V. Burgen, M.D. (Lond.), M.R.C.P., and N. G. Emmelin, M.D.(Lund). (Pp. 279 + vii; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1961.

***Emotional Factors in Public Health Nursing. A Casebook.*** Prepared by the Wisconsin State Board of Health. Editor: Abraham B. Abramovitz. (Pp. 171 + ix. $4.) Madison, Wisconsin: The University of Wisconsin Press. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY JULY 8 1961

## HUMAN WAREHOUSES

The Birmingham Regional Hospital Board is to be congratulated on publishing a report on its geriatric services[1] which it might have retained as confidential. The author of the report, Dr. J. H. Sheldon, of Wolverhampton, can speak with authority and from unrivalled personal experience. In this excellent document he shows a state of affairs which is highly unsatisfactory and which the Board acknowledges. What had to be said is said with eloquence and candour, and the chief source of the defects is made plain : it is the legacy of sombre old "chronic-sick" hospitals acquired in 1948. Some of these are hospital slums which by and large "do no more than provide storage space for the patients under conditions of considerable difficulty, and often unpleasantness, for the nursing staff." In the days when these ancient places were built patients were always nursed in bed, there was no thought that they needed recreation or could be restored to activity, and the bedpan was the answer provided for all their toilet problems.

Geriatric medicine is now undergoing a revolution, often, as Dr. Sheldon so plainly shows, in the face of appalling deficiencies of accommodation, staff, and services. The revolution is timely, because old age is likely to provide the hospital service with its principal challenge in the next twenty years. When are the hopelessly inadequate buildings in use to-day going to be replaced? Sheldon paints a doleful picture of the conditions in many of the Birmingham Region's establishments, and says that in five of them the accommodation is so deplorable that they are fit for nothing but demolition and replacement. New buildings are also needed in other places to cater for local needs. The basic structure of many hospitals makes it difficult to find the space vitally needed for dayrooms, physiotherapy departments, and modern sanitary facilities. What is true of one region is undoubtedly true of most others. It is not generally realized that many hospitals for the chronic sick are over 100 years old, some have stood for 200 years, and very few of them had had significant modification before 1948. In spite of this, in the Birmingham Region only one-sixteenth of the expenditure on capital works has been allotted to hospitals for the chronic sick, though they contain one-seventh of the total beds.

In the last ten years many management committees up and down the country have made determined and successful efforts to brighten and improve geriatric hospitals by paint and patchwork. But this is not enough. It is scarcely credible that in 1961 we have scores of hospitals caring for very disabled elderly patients without the benefit of a passenger lift. Sick people have to be manhandled upstairs, and once on the upper floors they may be marooned there for the rest of their days, and often at considerable risk from fire. New geriatric centres with full diagnostic facilities and provision for active treatment are badly needed, but present-day hospitals must also provide services which are social as well as technical if the younger generation is to be helped to care for their elderly relatives. Day hospitals are one solution to this problem. Sheldon also suggests that there is a need for long-stay annexes in small centres of population, perhaps in association with the cottage hospitals. In the medical staffing of geriatric hospitals, especially the outlying ones, there is great scope for the general practitioner, provided he is really interested in the treatment of elderly people. It is important that he should have acquired some experience of the methods of a geriatric unit and have the guidance of a specialist physician.

In considering the geriatric services provided in the region's hospitals, including medical, nursing, almoner, and physiotherapy services, Dr. Sheldon makes the point that a low level of expenditure may not mean that the hospitals are being economically managed but rather that they are deficient. Workers will not be attracted into a field where the working conditions are notoriously poor. Clearly the heart of the matter is bad hospital buildings, and a large programme of new construction is a prime necessity. In an attempt to minimize the huge cost of new buildings a working party at Birmingham has designed a standard geriatric ward unit which could be set up quickly where the need was greatest. Dr. Sheldon's work will no doubt stimulate other regions to re-examine their own geriatric services in the same admirably critical light, and if they do so they will almost certainly be forced to appeal urgently to the Minister for help in correcting a situation which is a discredit to the hospital service and a reproach to our age.

[1] Sheldon, J. H., *Report to the Birmingham Regional Hospital Board on its Geriatric Services*, 1961. Published by Birmingham Regional Hospital Board, 10 Augustus Road, Birmingham 15.

## LATENT BRUCELLOSIS

Like many infections brucellosis is seen in an acute form, a chronic form, and as a latent or "inapparent" infection. Description of the acute form as a specific fever came first, and owing to the striking character of the pyrexia this is still widely known as undulant fever. The chronic form is often a long-continued illness of insidious onset and with a tendency to recurrent exacerbations, whose chief symptoms are excessive and usually nocturnal sweating, lassitude, and joint pains; pyrexia is low, irregular, or absent. In chronic brucellosis the diagnosis is often missed; blood cultures are rarely positive; serum agglutination of *Brucella abortus* is not necessarily associated with clinical symptoms, nor is a brucellin skin test. The condition is more common in those over than under 40, and in agricultural districts than in towns; a history of drinking raw milk or of prolonged contact with farm animals may be a valuable clue. Unpasteurized milk is well known to be a cause of both *Br. abortus* and *M. tuberculosis* infection, even when the milk is derived from tuberculin-tested attested herds. The possible danger of contracting tuberculosis from such a source was recently pointed out in a report published in this journal.[1] The chronic form of brucellosis is particularly associated with strains of *Br. abortus*, which, with rare exceptions, is the only type of the organism found in Britain.

Evidence that latent brucellosis may be more common than is usually supposed has been strengthened by epidemiological studies, including agglutination and skin testing, on farmers, farm workers, and veterinarians[2 3]; and in this issue Drs. Ian McWhinney and A. P. Prior (p. 80) describe a study of this kind on 20 farm-worker volunteers from one general practice in Warwickshire, none of whom had a history of undulant fever. The brucellin test was found to be very strongly positive in five, strongly positive in five, positive in one, and negative in nine. Antibodies to a *Br. abortus* antigen were present initially in a titre of 1:40 or more in eight (five of whom had also a strongly positive skin test), and a second agglutination test two to three weeks later was positive in ten, of whom eight showed a rise in titre. Careful inquiry into past histories then elicited the information that two of the volunteers had had undiagnosed illnesses, one ten years previously and the other 25 and 11 years previously, which by their description were almost certainly acute or chronic brucellosis. On the evidence of the two tests combined and the common history of work on farms, it would appear that 14 out of 20 (70%) of farm workers in a district of mixed arable and stock farming had been infected with *Br. abortus*, 12 having had no recognized symptoms and two having had previous undiagnosed illnesses which were probably brucellosis.

W. Dalrymple-Champneys[4] has long contended that the real incidence of brucellosis is considerably higher than the reported incidence; and this fresh evidence of latent and undiagnosed brucellosis should make for increased awareness of the condition by doctors in agricultural districts, especially if a patient with pyrexia of unknown origin presents with symptoms of sweating, malaise, or limb pains.

[1] Black, J. M., and Sutherland, I. B., *Brit. med. J.*, 1961, **1**, 1732.
[2] Arbiaster, P. G., and Prior, A. P., *Vet. Rec.*, 1956, **68**, 969.
[3] Damon, S. R., Scruggs, J. H., and Parker, E. B., *J. Amer. vet. med. Ass.*, 1950, **117**, 39.
[4] Dalrymple-Champneys, Sir W., *Brucella Infection and Undulant Fever in Man*, 1960. Oxford Univ. Press, London.

## PULMONARY EMBOLISM

The surgical treatment of pulmonary embolism has interested surgeons since the publication of Trendelenburg's original paper in 1908,[1] but the successful results published since then have been disappointingly few. P. R. Allison and colleagues[2] have recently drawn attention to the importance of the question, for they record 70 cases of pulmonary embolism as the cause of death in 838 necropsies (8%) on patients at the Radcliffe Infirmary, Oxford, in 1957. It would seem that with the advent of modern cardiac surgery, and the use of methods such as hypothermia and cardiopulmonary by-pass, better results should now be obtained, and Allison and his colleagues report the successful surgical treatment under hypothermia of a severe case of pulmonary embolism.

If the patients can be got to a thoracic unit in good time, the operation they describe should be repeatable more often. The difficulty, as always, is the diagnosis of pulmonary embolism. The cases probably fall into three groups. The first is sudden massive embolism without warning; usually the course of events is so rapid that nothing can be done to avert the patient's death. The second, and probably the largest group, includes patients in whom the symptoms of the pulmonary emboli are obscured by previous severe illness or major surgical procedures; the emboli are found at post-mortem examination. These patients are usually diagnosed as having terminal bronchopneumonia and die quietly without typical symptoms; the lung shadows are not diagnostic of an infarct but are usually consistent

[1] Trendelenburg, F., *Zbl. Chir.*, 1908, **35**, 92.
[2] Allison, P. R., Dunnill, M. S., and Marshall, R., *Thorax*, 1960, **15**, 273.
[3] Lewis, I., *Modern Trends in Cardiac Surgery*, 1960, p. 56, Butterworth.
[4] Marion, P., Tartulier, M., and Deleuze, R., *Sem. Hop. Paris*, 1953, **29**, 4048.
[5] Dible, J. H., *J. Path. Bact.*, 1958, **75**, 1.

with a diagnosis of basal bronchopneumonia. The third group includes cases in which there is a definite, fairly long history and sometimes an obvious cause. It is this group of patients to which special attention should be directed, because some of them ought to be successfully treated.

Owing to the difficulties of remedial treatment, prophylaxis is of paramount importance in this condition. The best prophylactic treatment is anti-coagulation, but it is difficult to decide when to start. Opinions vary from giving anticoagulants to every patient post-operatively with physical signs in the legs, to giving them only to patients who have distinct signs of pulmonary embolism. This treatment is relatively simple and has the great advantage of not disturbing the patient unduly. If it is unsuccessful, ligation of veins has to be considered, but the choice of which veins should be ligated, and where, may be difficult. Ideally the inferior vena cava may be best, but ligation of this is a procedure which no surgeon embarks on with enthusiasm. The operation is safer if carried out at the level of the external iliac veins or, in some cases, perhaps even the common iliac veins. As to treatment of pulmonary embolism itself, I. Lewis[3] has described several approaches. One of the easiest is to try to remove the clot through the left main pulmonary artery by means of a left-sided incision, rather than doing the original Trendelenburg operation into the pulmonary trunk. It was successfully used in two cases by P. Marion and his colleagues.[4] If there is time, the ideal method of approach is the vertical sternal incision with occlusion of the superior and inferior venae cavae, thus giving the surgeon an empty heart; in this way the pulmonary trunk can be opened and the clot removed. Hypothermia will give at least eight minutes for this manœuvre, and the point made by Allison and colleagues that the clot sometimes cannot be sucked out of the distal branches but has to be removed with forceps is very important, for this may take all the time available. Lewis has also investigated the size and diameter of the emboli that come up the inferior vena cava, and has developed a clip to place round it just below the renal veins to convert the vena cava into an oval tube not more than 5 mm. in antero-posterior diameter. In his experience fatal pulmonary emboli are over 7 mm. in diameter, and thus cannot pass the clip. The clip can be removed at a later date.

Allison and his colleagues also report an investigation into whether non-fatal pulmonary emboli are completely absorbed, and this work was carried out in the dog. The most important point they make is that the size of the clot found at necropsy may be a poor indication of its size when it first reaches the lungs. By four days the clot was much smaller, and fairly soon "endothelium" started to grow over it. At the same time there was a striking dilatation of the vessels in the adventitia adjacent to the point of attachment. The clot progressively diminished in size and by 21 days was no longer recognizable in the elastic pulmonary arteries, though there were persisting focal areas of subintimal fibrosis. These workers concluded that the whole process was one of organization rather than canalization, as emphasized by J. H. Dible.[5] By 28 days even the fibrous nodules had disappeared and there was an apparently normal vascular tree. Allison and his colleagues conclude that, if the experimental results are applicable to the clinical problems of pulmonary emboli in man, the most important deduction is that we cannot yet diagnose clinically a pulmonary embolism "unless it occurs either in the presence of previous severe pulmonary artery obstruction, or in the presence of pre-existing pulmonary venous congestion." They suggest that numerous small emboli undetectable by any normal means may precede a major embolism, and that only when a sufficient degree of obstruction to the pulmonary circulation has occurred would a further single embolus of moderate size cause the sudden symptoms that are observed clinically. This would fit in with pathologists' findings that in patients dying of pulmonary embolism smaller organizing thrombi are nearly always found.

The main question that remains unanswered is why apparently some emboli when they reach the lungs are rapidly absorbed and give rise to no symptoms, whereas others become impacted as plugs at various levels in the pulmonary tree and cause either infarcts or, when in the very large vessels, the death of the patient. A possible aetiological factor is the presence of stasis in the circulation. As Allison and colleagues point out: "It might well be, therefore, that the problem of pulmonary embolus is not the prevention or treatment of the single massive thrombus, but the counteracting of a process that is going on all day and every day as a natural result of operation."

## RESUSCITATION OF THE NEWBORN BY COOLING

The multiplicity of methods advocated for resuscitation of the newborn shows that no one is manifestly superior to all others. Fortunately the majority of infants breathe spontaneously within a few seconds of birth, and, apart from ensuring a clear airway, no active measures are needed. But, in the minority where spontaneous respiration is slow in starting, the choice

of a method of resuscitation becomes increasingly urgent as time passes. In making a choice the efficiency of the proposed method has to be balanced against the risk of damaging the infant. Generally the infant in blue asphyxia, with a strong rapid heart-beat, fair muscle tone, and responding to cutaneous stimuli, is not in immediate danger and should not be subjected to such potentially dangerous procedures as vigorous manual stimulation, the injection of analeptics, or laryngeal intubation with positive-pressure respiration. But asphyxia is never static, and some infants pass into white asphyxia. Some are in this state at birth. Pale and limp, with a slow heart-rate and no response to cutaneous stimulation, they look—and are—half-dead. This calls for a more vigorous method, usually some form of positive-pressure respiration if available.

Other forms of resuscitation have their advocates, and the successful treatment of six babies in white asphyxia by means of hypothermia is reported by B. Westin and colleagues from Stockholm.[1] Other methods of resuscitation having failed, these infants were placed in cold running water and the colonic temperature allowed to fall to between 23 and 30.4° C. (73 and 87° F.). In three cases spontaneous respiration started during cooling and no further treatment was required, though the babies were kept cool for several hours afterwards. In the other three a transfusion of oxygenated blood was given in addition because hypothermia alone had proved ineffective ; improvement followed rapidly. Five infants made an apparently complete recovery, though the follow-up period at the time of writing was short. One died on the second day.

Both types of treatment, hypothermia and transfusion of oxygenated blood, are founded on the convincing results of experiments on newborn animals and on pre-viable human foetuses. Anoxic newborn guinea-pigs survive longer if chilled than if kept at room temperature.[2] The survival time of pre-viable human foetuses is increased by keeping them at 25° C. (77° F.) instead of 37° C. (98.4° F.).[3] Perfusion of oxygenated blood increases it still further.

Yet the rapidity of the response to cooling shown by the first three cases reported by Westin and colleagues suggests that increased tolerance to anoxia at a low temperature is an insufficient explanation of the good results. In two cases gasping occurred when the body temperature was still fairly high, and it was preceded by improvement in skin colour and muscle tone. These observations suggest that cold acted as a stimulant, though in white asphyxia any response is surprising. The authors suggest that cold has a direct vasoconstrictor effect on the blood-vessels, acting independently of the nervous system, and thus counteracts the general vasodilatation of shock. This is a reasonable hypothesis, for it explains the failure of stimulation by cold water on the skin to produce general vasoconstriction ; such general vasoconstriction would require the operation of vasomotor reflexes, which are unlikely to act in white asphyxia. However, if cold acts on blood-vessels directly, then it is only when both deep and superficial blood-vessels are chilled—that is, during hypothermia—that vasoconstriction will be sufficiently generalized to raise the blood-pressure, increase cardiac output, and reverse the deterioration of the infant's general condition.

Deliberate chilling of newborn infants is unlikely to find general favour at present, especially now that the dangers of accidental exposure to cold are realized.[4–6] Nevertheless, it is reasonable to try it in infants with white asphyxia who have failed to respond to other methods. It requires no special apparatus and appears to be less dangerous than some other procedures. Emergency transfusion of oxygenated blood is another matter, for this will seldom be practicable as an emergency measure.

[1] Westin, B., Miller, J. A., Nyberg, R., and Wedenberg, E., *Surgery*, 1959, **45**, 868.
[2] Miller, J. A., Jr., and Miller, F. S., ibid., 1954, **36**, 916.
[3] Enhorning, G., and Westin, B., *Acta physiol. Scand.*, 1954, **31**, 359.
[4] Mann, T. P., and Elliott, R. I. K., *Lancet*, 1957, **1**, 229.
[5] Bower, B. D., Jones, L. M., and Weeks, M. M., *Brit. med. J.*, 1960, **1**, 303.
[6] Ibid., 1960, **1**, 408.

## EXPERIMENTAL GLAUCOMA

Ophthalmologists in India noted in the early years of the century that in outbreaks of epidemic dropsy many patients showed glaucoma. An incidence of glaucoma as high as 30% has been reported for some epidemics, though the evidence is not convincing, and it is also not clear whether the glaucoma always occurred during the epidemic or later. In 1926 S. L. Sarkar[1] held that these epidemics were due to the contamination of cooking oils with the seed of the common prickly yellow poppy, *Argemone mexicana* L. Experimental evidence in favour of this view is not very definite, and it is of interest that, though R. B. Lal and his associates[2] obtained oedema in two series of volunteers fed with argemone oil, they failed to obtain glaucoma. In recent years the work of S. N. Sarkar[3] and of S. A. E. Hakim[4 5] has concentrated on the isoquinoline alkaloid sanguinarine as the possible toxic factor in argemone oil. Hakim claimed that subconjunctival injection of either argemone oil or sanguinarine in rabbits and monkeys increased the intraocular pressure. Some supporting evidence has come from E. H. Leach and J. P. F. Lloyd,[6] who reported the induction of chronic hypertension in monkeys by prolonged feeding with sanguinarine. But G. C. Dobbie and M. E. Langham[7] failed to obtain any change in intraocular pressure or any histological changes from feeding sanguinarine to rabbits, cats, and hens. These observers did obtain a rise in intraocular pressure in the rabbits and the cat by the injection of sanguinarine either intravenously or into the lateral ventricle, but unlike Hakim they could not obtain any persistent rise in pressure, and such rise as they obtained was related to a change in the systemic blood-pressure. The relationship between the effects of

[1] Sarkar, S. L., *Indian med. Gaz.*, 1926, **61**, 62.
[2] Lal, R. B., Das Gupta, A. C., Mukherji, S. P., and Adak, B., *Indian J. med. Res.*, 1941, **29**, 839.
[3] Sarkar, S. N., *Nature (Lond.)*, 1948, **162**, 265.
[4] Hakim, S. A. E., *Brit. J. Ophthal.*, 1954, **38**, 193.
[5] —— *J. Physiol.*, 1957, **138**, 40.
[6] Leach, E. H., and Lloyd, J. P. F., *Trans. ophthal. Soc. U.K.*, 1956, **76**, 453.
[7] Dobbie, G. C., and Langham, M. E., *Brit. J. Ophthal.*, 1961, **45**, 81.
[8] Hakim, S. A. E., Mijovic, V., and Walker, J., *Nature (Lond.)*, 1961, **189**, 198.
[9] —— —— —— ibid., 1961, **189**, 201.

argemone oil and those of sanguinarine remains obscure. The experimental production of glaucoma, while of importance in gaining an understanding of the disease, does not necessarily have any direct bearing on its aetiology in the general population. However, S. A. E. Hakim and his colleagues[8 9] have suggested that glaucoma, as seen in the general population in India at any rate, may in fact be conditioned by a dietetic contamination. They report that they found sanguinarine in 49 out of 53 available species of poppy-fumaria weeds (i.e., Papaveraceae and Fumariaceae) they examined, and they held that it is likely that this alkaloid is probably present in many more of the 675 species of this vast alkaloid family with its world-wide distribution. They point out the evident danger from contamination of milk and other foodstuffs, and also from the traditional use of poppy-fumaria products in various parts of the world, particularly their inclusion in medicaments. In spite of these findings the question for the present is not only whether sanguinarine plays any part in the production of glaucoma in man, but whether indeed it is capable of exciting anything comparable to human glaucoma in the experimental animal.

## MEDICAL GEOGRAPHY OF MULTIPLE SCLEROSIS

The renewed interest in medical geography, recently referred to in this journal,[1] is already producing some stimulating results. A recent supplement of *Acta Psychiatrica Scandinavica*[2] is largely devoted to a "geo-medical conference" on the epidemiology of multiple sclerosis. Taken as a group, the papers restate (among other things) the known fact that this disease is more prevalent in northerly parts than near the equator. Two new explanations for this are offered, however. First, J. S. Barlow[3] suggests that the precipitating factors may include cosmic rays. He points out that the intensity of these increases with latitude, and indeed shows that for all countries in which the mortality is lower than that in Canada and England and Wales (which he treats as unity in calculating relative mortality rates) there is a correlation between deaths from multiple sclerosis and geomagnetic latitude. Two difficulties about his theory are that the variation in cosmic rays with latitude at sea level is negligible—as he himself shows—and secondly that the correlation does not hold at all for places where the mortality is higher than that in Canada and England and Wales.

The second paper, which appears to be less open to criticism, is included in the supplement, though it was not given at the symposium. It is one of two[4 5] from the U.S. Veterans Administration by E. D. Acheson and C. Bachrach. They show that the place of residence in childhood may possibly be of greater importance in the causation of the disease than residence at the time of admission to hospital. These authors also suggest that lack of solar radiation during the winter months may explain the known correlation with latitude. Their study is concerned with a random sample of 1,782 patients, 7.4% of whom were of negro extraction, discharged from Veterans Administration hospitals during 1954–8 with a firm diagnosis of multiple sclerosis. A steady and highly significant gradient of incidence of the disease from north to south was found. Of the "veterans" from outside the U.S.A., the ratio of observed to expected was about 10 times higher among Canadians than among those from Mexico and the Caribbean. All races studied appear to respond in the same way to the environmental differences between north and south. Significant correlations (r) were found between the frequency of multiple sclerosis and the following meteorological observations at the patient's birthplace: latitude (+0.76), average annual hours of sunshine (−0.73). December solar radiation (−0.80), and an index of the intensity of the winter cold (+0.67); neither annual precipitation nor maximum July temperature correlated significantly, however. Correlations between some of these factors and the length of stay at the place of residence before admission were also significant but much lower. Further analysis showed that the negative correlation with December solar radiation is the most impressive. The authors point out that previous workers have observed that multiple sclerosis is more prevalent in high than low latitudes, but they claim to be the first to draw attention to the possible role of sunless winters in early life. They add that the ultra-violet band of light is unlikely to be involved, because the incidence of multiple sclerosis is no higher in urban than in rural areas. For this reason they feel that a direct protective effect of sunshine (for example, on the skin) is unlikely, and that, if solar radiation is important, it is more likely to act indirectly through the plant or animal environment.

## THE EMOTIONS AND ELECTROLYTES IN HEART FAILURE

Emotional stress has been blamed for precipitating or aggravating congestive heart failure. W. N. Chambers and M. F. Reiser[1] related the onset of cardiac failure to emotional disturbance in 19 out of 25 patients, noting that stimuli which caused rage, frustration, anxiety, depression, or feelings of insecurity apparently did much to precipitate congestive heart failure. Retention of sodium and water during periods of emotional tension or depression, followed by a diuresis after relaxation of the emotions, has also been reported.[2] R. Barnes and W. W. Schottstaedt[3] have reported studies in eight male subjects who had recently suffered from congestive heart failure. None were in failure at the time of study, and metabolic investigations were carried out for periods ranging from 14 to 45 days Intake and output

[1] *Brit. med. J.*, 1960, **1**, 1950
[2] *Acta psychiat. scand.*, 1960, **35**, Suppl., 147.
[3] Barlow, J. S., ibid., 108.
[4] Acheson, E. D., and Bachrach, C. A., *Amer. J. Hyg.*, 1960, **72**, 88.
[5] —— —— and Wright, F. M., *Acta psychiat. scand.*, 1960, **35**, Suppl., 147, 132.

of fluid and electrolytes were measured, and at the same time records were kept of emotional changes, variations in mood, and psychological reactions to other patients and to medical staff. Assessments of the patients' psychological and emotional states were kept separate from the biochemical studies and not related until the investigations were completed.

The patients proved to be highly sensitive to any suggestions about the prognosis of their heart disease. Emotional tension and depression were associated with a decrease in excretion of sodium, of total urine and, to a lesser extent, of potassium. By contrast, reassurance, relaxation of emotional tension, and lifting of depression were followed by increased excretion of sodium and water. Periods of excitement, apprehension, agitation, or anger were associated with a greater output of sodium and water as compared with tranquil periods, but potassium output was not significantly increased.

The effects of body position and physical activity were specially studied in four patients. Urinary volume and sodium excretion decreased on walking as compared with resting in the sitting or recumbent position. This response was altered by great emotional stress: often patients appeared more relaxed while sitting than lying, and when this was so the output of sodium was greater in the former than in the latter position. Emotion sometimes seemed more important than physical activity in determining sodium output, which in one subject was thirty-two times greater during strenuous activity than during a period of sitting when in a tense and anxious frame of mind. Patients with heart disease retained less water during periods of emotional tension than normal subjects, though there was significant retention of sodium. The patient who had suffered the most severe congestive heart failure in the series showed no alteration in urinary volume during periods of psychological tension, though excretion of sodium was reduced. The authors of this paper speculate on the possible effects of increased secretion of antidiuretic hormone in this context, for increased secretion independent of osmoreceptor control in congestive heart failure[4] might render the patient less susceptible to variation in water excretion resulting from other stimuli. They also consider that increased secretion of aldosterone as a result of emotional stress might possibly account for the reduced urinary volume and sodium excretion.[5–7]

This careful study deserves attention and may explain the sometimes inexplicable failure of patients with congestive heart failure to improve on accepted treatment. But other than psychological factors may have been at work, too. Haemodynamic studies of cardiac output and work during periods of emotional tension would have been of interest, while emotional states may be less easily measured and analysed than are physical and biochemical disorders. No mention is made of hyperventilation as a possible factor in producing alterations of electrolytes. More work on this important subject will clearly be necessary, but in the meantime it is worth remembering that attention to psyche as well as to soma is important in the treatment of heart disease, and in particular of congestive heart failure.

[1] Chambers, W. N., and Reiser, M. F., *Psychosom. Med.*, 1953, **15**, 38.
[2] Schottstaedt, W. W., Grace, W. J., and Wolff, H. G., *J. psychosom. Res.*, 1956, **1**, 75, 147, 203, 287.
[3] Barnes, R., and Schottstaedt, W. W., *Amer. J. Med.*, 1960, **29**, 217.
[4] Hanenson, I. B., Goluboff, B., Grossman, J., Weston, R. E., and Leiter, L., *Circulation*, 1956, **13**, 242.
[5] Luetscher, J. A., Jr., and Lieberman A. H., *Trans. Ass. Amer. Physcns*, 1957, **70**, 158.
[6] Lamson, E. T., Elmadjian, F., Hope, J. M., Pincus, G., and Jorjorian, D., *J. clin. Endocr.*, 1956, **16**, 954.
[7] Venning, E. H., Dyrenfurth, I., and Giroud C. J. P., ibid., 1956, **16**, 1326.

## DR. ALBERT SCHWEITZER, Hon.O.M.

The Council of the B.M.A. recently invited Dr. Albert Schweitzer to become a Foreign Corresponding Member of the Association. Our readers will be glad to learn that Dr. Schweitzer's charming letter of acceptance came from Lambaréné in his own firm handwriting. It runs as follows:

Lambaréné—Gabon
Afrique Equatoriale Française

Monsieur le Secretary de British Medical Association, British Medical Association House, Tavistock Square, London W.C.1. 28 mai, 1961

Monsieur le Secrétaire,

Je vous accuse réception de votre lettre du 15 mai, dans laquelle vous me faites savoir que le Council of the British Medical Association me nomme Foreign Corresponding Member de l'Association. Je remercie le Council du grand honneur qu'il me fait et j'en suis profondément touché.

J'accepte aussi avec joie et grande reconnaissance, de recevoir régulièrement le *British Medical Journal*, dont je connais la renommée. Un de mes médecins anglais y était abonné et nous avons bénéficié de le lire avec lui. Les quatre médecins qui travaillent avec moi ici savent très bien l'anglais et se réjouissent d'avoir à leur disposition ce célèbre journal médical. Mon hôpital marche bien. Nous sommes 5 médecins et 15 nurses européennes.

Veuillez transmettre l'assurance de ma profonde reconnaissance à Messieurs les Membres du Council.

Avec mes bonnes pensées,
votre dévoué ALBERT SCHWEITZER.

Dr. Schweitzer requested one of his Dutch nurses, Miss A. C. Silver, to translate his letter, and this she has kindly done, asking to be excused for any imperfections in her English.

Dear Sir,

I acknowledge receipt of your letter, dated May 15th, in which you write me, that the Council of the British Medical Association invites me to be Foreign Corresponding Member of the Association. I thank the Council so much for the honour and I feel deeply touched by it.

I also accept with great pleasure the regular receipt of the *British Medical Journal*, which has such a good renommée. One of my English doctors received it and so we had the advantage to read it too. My four doctors have a good knowledge of the English language and are looking forward to having at their disposal your famous journal. All is well at the hospital: we are five doctors and 15 European nurses.

Please, kindly express my deep gratitude also to the members of the Council.

With my kind thoughts,
Devotedly yours,
(signed) ALBERT SCHWEITZER.

# New Appliances

## A METHOD OF APPLYING TRACTION TO THE CHEST WALL

Dr. J. A. MILLIGAN, Stobhill General Hospital, Glasgow, writes: There has been a steady increase in the incidence of serious chest injuries in recent years. The basic principles of treatment have been established, and it is agreed on all sides that early and adequate ventilation is a prime factor. Majority opinion favours the use of controlled respiration after intubation, but surgical treatment is still required in the presence of serious intrathoracic injury and flail-chest with gross paradoxical respiration. There is some doubt about the best method of immobilizing the chest wall and the indications for surgery for this purpose. However, it is clear that sometimes, with or without operative fixation of ribs and sternum, it is necessary to employ traction to control paradoxical respiration. The purpose of this contribution is to describe an apparatus we have designed and which we believe to be an effective method of immobilizing the sternum.

Such an apparatus should be simple to apply, adaptable to different types of fractures of the sternum, stable after application, and non-traumatizing to the tissues. An attempt has been made to meet these requirements in the design.

The equipment consists of a pair of articulated tongs (Fig. 1), the blades of which can be disengaged and inserted separately as with obstetric forceps. The sharp points of the clips are driven into the sternum through a small incision in the skin and fixed by a ratchet or screw clip. In this way soft-tissue trauma is minimized (Fig. 2). After insertion and articulation the two tongs are linked by a metal rod which provides rigidity and prevents rotation. The metal rods are supplied in various sizes, so that the correct length may be selected to bridge the distance between the tongs, which are inserted in the intercostal spaces. A metal loop is fitted to the mid-point of the connecting rod, and traction is effected by threading a nylon cord through this loop.

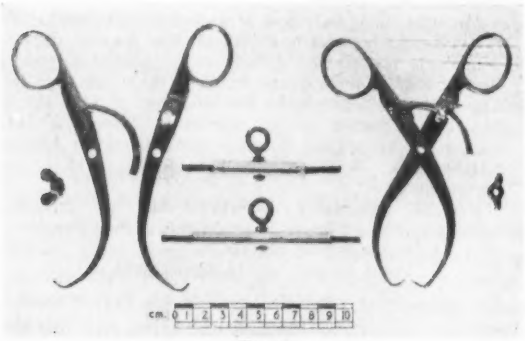



FIG. 1

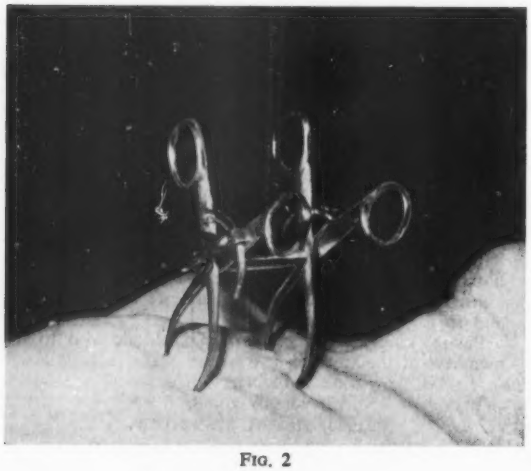


FIG. 2

The application of traction has presented difficulty in the past. A variety of methods have been used, such as plaster-of-Paris casing, bed cradles, Balkan frames, etc., but it is difficult to achieve stability with adjustability and at the same time allow free access for nursing attention. In this unit such cases are nursed in the recovery room, where special trolley beds and other facilities are available, and a suspension rod has been designed which can be readily fitted into a socket in the side of the trolley. The mechanism consists of a tube ($\frac{5}{8}$ in.; 1.6 cm.) bent to a right angle which can be raised, lowered, or rotated as required. A solid rod with pulley attached is inserted into the open end of the tube and locked with a thumb-screw. It can therefore be rotated in its long axis or telescoped into the hollow tube. It is thus possible to make adjustments so that the pulley can be situated in any position above the patient and direct traction can be effected in precisely the required direction (Fig. 3). Traction of the order of 10–14 lb. (4.5–6.4 kg.) may be necessary, but by using a double pulley the load attached to the cord is halved.

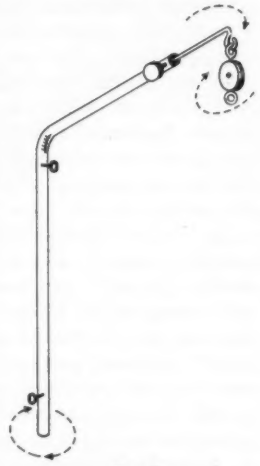


FIG. 3

This equipment is compact. There are no overhead beams or cords and it is easily adjusted to the changing position of the patient. The suspension rod may be used for any situation requiring an adjustable pulley system.

I am indebted to Mr. John Hutchison for allowing me to publish this article, and for his great help and encouragement in designing the apparatus. My thanks are also due to Mr. James Strachan and his assistant, Mr. Victor Ba Maung, engineers, Stobhill General Hospital; to Mr. P. S. Waldie, hospital clinical photographer, for the photographs; and to Mr. H. Dawson, architect, for the drawing.

This apparatus is to be produced by Charles F. Thackray Ltd., of Leeds, and a bedside clamp will be available so that the suspension rod may be attached to any hospital bed.

---

Dulwich House was recently opened in Cardiff for the Board of Governors of the United Cardiff Hospitals. The building, known as the Lord Pontypridd Hospital, was formerly used for the care of children suffering from rheumatic heart disease. In 1960 the Board of Governors, who administer the hospital, agreed that it should be adapted for the care of patients—aged approximately from 15 years to 50—with chronic neurological disorders. Extensive renovations were made and there is accommodation for 20 patients, most of whom suffer from multiple sclerosis. There is a fully equipped physiotherapy department, three acres of lawns and gardens, and all the appropriate equipment for caring for disabled patients. The hospital is being used to provide symptomatic treatment, rehabilitation after a first attack or relapse of multiple sclerosis, and temporary care of the very seriously disabled so that relatives can have a rest. Dr. J. D. Spillane is the consultant neurologist.

# To-day's Drugs

*With the help of expert contributors we publish below notes on a selection of drugs in current use.*

**"Nystatin"** (E. R. Squibb and Sons).

*Composition.*—Nystatin is an antibiotic derived from cultures of *Streptomyces noursei*. In powder form it is unstable in the presence of moisture, and should be kept tightly closed in a cool place.

*Pharmacology.*—Nystatin inhibits many species of yeasts and fungi, but its most important property is its pronounced action against *Candida albicans*. It is not absorbed to any great extent from the alimentary tract, and so is only of slight value in systemic candida infections.

*Therapy.*—Nystatin controls candida infections wherever it can be applied topically, probably more effectively and less unpleasantly than gentian violet. The common sites of skin infection with candida, to which diabetics are especially prone, are the vulva, the perineum and groins, under the breasts, the corners of the mouth, the clefts between the digits, and the nailfolds. In all these places nystatin ointment (100,000 units per g.) is a suitable application; alternatively nystatin dusting powder (100,000 units per g.) may be used in intertriginous areas. Vulval lesions may be secondary to a vaginal infection, and for this nystatin vaginal tablets (each containing 100,000 units) should be inserted twice a day for a fortnight. Perineal involvement, and possibly lesions elsewhere such as perionychia, may be associated with infection of the alimentary tract, which may follow treatment with broad-spectrum antibiotics; for this nystatin oral tablets (500,000 units) should be given three times a day by mouth. For systemic candidiasis 2 oral tablets four times a day or even more have been advocated, but it is much less effective than amphotericin B, which, however, must be given intravenously.

The buccal mucosa may show "thrush," which should be looked for in all patients with angular stomatitis; for this nystatin oral tablets may be sucked four times a day. Otitis externa may be due to candida more frequently than has been realized[1]; possibly here again it may be the sequel to the local use of antibiotics. The recommended treatment is to keep the ear clean and dry and insufflate nystatin dusting powder.

*Side-effects.*—Nystatin by mouth is only slightly absorbed and is thus non-toxic. Local application has not so far been reported as causing sensitization, but sooner or later this will probably occur.

*N.H.S. Basic Price.*—½ oz., 7s.

REFERENCE

1 Gregson, A. E. I. J., and La Touche, C. T., *J. Laryng.*, 1961, 75, 45.

**"Crolax"** (Crookes Laboratories).

*Composition.*—This preparation contains equal parts of dioctyl sodium sulphosuccinate, which has a detergent-like action, and 1,8-hydroxyanthraquinone, the action of which resembles that of the anthracene purgatives, which depend largely on anthraquinone for their activity. One tablet contains 50 mg. of each of these constituents.

*Therapy.*—That the preparation will have a laxative action largely exerted on the colon is clear from the presence of the hydroxyanthraquinone. So far as is known, no unwanted effects arise from the use of such detergent-like substances as the other constituent of the preparation. In fact, it is incorporated in order to facilitate the passage of fluid through the intestinal contents and thus encourage the formation of a homogeneous and soft faecal mass. Crolax takes its place in efficacy between simple lubricants on the one hand and purely purgative substances on the other, which are liable to cause griping. The dose for adults is two tablets at night and for children one tablet at night.

*N.H.S. Basic Price.*—100 tabs., 5s. 6d.

# Correspondence

*Because of heavy pressure on our space, correspondents are asked to keep their letters short.*

## Canvassing in Medical Elections

SIR,—Mr. Franklyn Stonham (June 24, p. 1829) has criticized the practice of canvassing in elections to "some body such as the council of the Royal College of Surgeons," and he has been in communication with the College on the subject. Your readers may like to know that this question has often been discussed by the council of the College, who from time to time have expressed their disapproval of various forms of canvassing. I am instructed to say that the matter will again be considered before the date of the next election.

It would no doubt be possible to make rules about canvassing, but it would obviously be very difficult to enforce them. Whenever the council have made a pronouncement on the subject, they have always exhorted Fellows to use their independent judgment in voting. Perhaps this is the most effective way in which they can comply with Mr. Stonham's request to state their views.—I am, etc.,

Royal College of Surgeons,
London W.C.2.

KENNEDY CASSELS,
Secretary.

## Barium Studies in the Aged

SIR,—Drs. A. N. Exton-Smith and G. Osborne are to be congratulated on their careful and painstaking analysis of barium studies in the aged (June 24, p. 1799). Their appraisal of the value of the barium meal in the aged will, I feel sure, meet with general approval.

Much as one sympathizes with them in trying to avoid unnecessary barium enemas in the old and decrepit, their conclusion that too many of these examinations are being carried out is simply not justified by the facts. As they point out in their paper, of 123 consecutive cases of carcinoma of the colon admitted to the Whittington Hospital, no less than one-third had acute large-bowel obstruction. Haggie[1] reported similar findings from the London Hospital. Most of these patients with acute large-bowel obstruction due to carcinoma of the colon, however, are old or very old.[2] Because they mostly have small "string" carcinomas they have no palpable lump, nor do they pass blood in their stools. The growth is usually beyond the reach of the sigmoidoscope. In fact, the only means we have of diagnosing carcinoma of the colon in these old people, before they become obstructed, is by barium enema. The only symptom of which these old people complain before they become obstructed is increasing constipation and colicky abdominal pain, often coming on soon after meals. Because of the relation of the pain to meals, they are often considered to have a gastric rather than a colonic lesion, and so a barium meal and not a barium enema is carried out: thus the diagnosis is missed until acute large-bowel obstruction supervenes.[3]

If we are to make the diagnosis of carcinoma of the colon in these old people, before they become obstructed, we shall have to do more rather than fewer barium enemas. We need to be more alive to the possibility that old people with minimal symptoms may have a "string" carcinoma of the colon, if we are to

diagnose this most easily resectable of all abdominal neoplasms before life is threatened by the advent of acute obstruction.—I am, etc.,

Whittington Hospital,
London N.19. PAUL T. SAVAGE.

REFERENCES

[1] Haggie, M., *Lancet*, 1952, **1**, 21.
[2] Savage, P. T., *Brit. J. Surg.*, 1960, **47**, 643.
[3] Muir, E. G., ibid., 1956, **44**, 1.

SIR,—In assessing a patient with gastro-intestinal disturbance the present tendency to hasty reference for barium meal or enema examination is to be deprecated. Such action increases the already significant waiting-list for these procedures which are, moreover, increasingly expensive and time-consuming as techniques elaborate and improve. Furthermore, as Drs. A. N. Exton-Smith and G. Osborne indicate (June 24, p. 1799), the aged or frail patient may find the investigation an ordeal and occasionally, in the case of the barium enema examination, a peril. Nor can one disregard the recommendations of the Adrian Committee on reducing radiation dosage.

I agree with Drs. Exton-Smith and Osborne that tests for faecal occult blood give some guidance in the selection of cases for such examinations. Unfortunately they do not state which method they employ. The modern orthotoluidine tablet tests of the Ames Company (London) Ltd. are simple and inexpensive and their use makes for a rapid, efficient, and relatively inoffensive examination of the patient's faeces. They are therefore of particular value in the investigation of an iron deficiency anaemia which may be caused by gastro-intestinal bleeding.

In general practice such anaemias are often severe, and a search for occult blood loss will coincide with the administration of oral iron. As I previously indicated,[1] this is correct procedure with all preparations except ferrous fumarate tablets, which lead to the development of false-positive results in the faeces. Drs. T. D. S. Halliday and I. M. Cuthill substantiated this belief,[2] recorded the confusion which such misleading results had caused, and advised that published information on that preparation should carry a warning of this obstacle to its use. I have now appraised a newcomer to the field of iron therapy: a preparation of ferrous carbonate and ascorbic acid ("ferrodic"). This product also causes false-positive results for occult blood, *in vivo* and *in vitro*, with either the obsolescent benzidine test or the orthotoluidine tablet tests. In view of the experiences of Drs. Halliday and Cuthill, I feel that awareness of this fact may help to reduce the number of patients referred for barium examination.—I am, etc.,

Edinburgh 10. DAVID G. ILLINGWORTH.

REFERENCES

[1] Illingworth, D. G., *Brit. med. J.*, 1959, **2**, 1099.
[2] Halliday, T. D. S., and Cuthill, I. M., ibid., 1960, **2**, 1310.

## Antimony and the Heart

SIR,—Your annotation, "Antimony and the Heart" (June 10, p. 1665), very properly underlines the possibility of cardiovascular damage following treatment of schistosomiasis with trivalent antimonial substances. To this may be added the possibility of liver damage. While few would disagree that tartar emetic or antimony sodium tartrate *given in the classical course* are the most active (and most toxic) schistosomicides at present available, it must be appreciated that the conditions under which they are used materially affect their efficacy and practical value in treatment.

In areas endemic for schistosomiasis, hospital facilities are usually grossly inadequate and only a small proportion of those requiring treatment can be admitted. The majority must be treated as ambulatory out-patients pursuing their normal occupations. Under these conditions, a thrice-weekly course of intravenous injections of tartar emetic may extend over four weeks. Cardiovascular toxicity apart, the side-effects are frequently severe, the interruption to earning capacity is considerable, and, unless under compulsion, many patients may fail to complete the prescribed course. The over-all efficacy of tartar emetic may be seriously affected by the lengthy course of treatment and the severity of side-effects.

Unlike bacteria, schistosomes do not multiply within the body and, in general, the pathological effects of the disease are related directly to the weight of infection and to its duration. Thus, in an endemic area where reinfection is likely, the virtue of striving after radical cure through the prolonged use of highly toxic drugs is open to doubt. It is in this context that the use of other trivalent antimonials such as sodium antimonylgluconate, B.P., may offer the advantages of reduction in length of treatment and reduced severity of side-effects, leading to a lower incidence of absenteeism and, consequently, a lower level of infection in the population under treatment.

The absence of more effective and less toxic schistosomicides is only too apparent, but, meanwhile, the need to treat demands the use of available drugs to best advantage in the prevailing circumstances. Trivalent antimony has been in use for the treatment of schistosomiasis for more than 40 years, but there is still need for controlled quantitative studies with the available preparations to define the least toxic and most effective regimen.—I am, etc.,

The Wellcome Laboratories
of Tropical Medicine,
London N.W.1. O. D. STANDEN.

## Cataract and Steroids

SIR,—Following a report by Black *et al.*[1] and also your annotation (January 14, p. 116) on the occurrence of posterior subcapsular lens opacities as a possible complication of steroid therapy; we have examined 98 asthmatic patients receiving steroids. Fifty-two of these had received prednisone or an equivalent analogue in a daily dose of 10 mg. or more for one year or more. Of these, 41 received continuous therapy for between one and three years and 11 for between four and nine years. All of these patients were examined under a mydriatic by ophthalmoscopy and slit-lamp microscopy.

One case only showed bilateral, posterior, polar, subcapsular cataracts. This was a female patient aged 60 years who had received more than 10 mg. of prednisone per day for three years. However, elsewhere, she had also been given many courses of gold intramuscularly in the treatment of her asthma. This may be relevant to the development of her cataracts. Moreover, in this case, in addition to subcapsular changes, opacities were present in the posterior cortex of the lens mainly localized to the axial region. Therefore the changes in this one case are of doubtful aetiology, nor quite typical of those described by Black *et al.*

Four other patients, all of whom were receiving prolonged steroid treatment of more than 10 mg. per day, showed minimal changes at the posterior pole amounting to coarsening of the pattern of the lens fibres. These changes have been seen in patients not receiving steroids and their significance is doubtful.

Apart from the 98 patients in the above group, two patients have been seen in the Eye Department for other reasons and found to have changes typical of those described by the American workers. Both of these patients were suffering from rheumatoid arthritis and had received large doses of steroids over periods of one year and four years.

Our findings would seem to indicate that from the point of view of cataract formation there is no contra-indication to the prolonged use of steroids in the treatment of asthma. The posterior subcapsular cataracts described by Black *et al.*, the single case found by Dr. F. Dudley Hart and his colleagues (June 10, p. 1680), and our two cases occurred in patients with rheumatoid arthritis treated with steroids. It is possible, therefore, that besides prolonged exhibition of steroids an additional factor in the disease process, perhaps peculiar to a collagenosis, is necessary for the development of this particular lesion.—We are, etc.,

University College Hospital, London W.C.1.

H. BADERMAN.
C. MAGUIRE.

REFERENCE

[1] Black, R. L., Ogelsby, R. B., von Sallmann, L., and Bunim, J. J., *J. Amer. med. Ass.*, 1960, **174**, 166.

## Prevention of Rh Haemolytic Disease

SIR,—Dr. Frank Marsh (June 10, p. 1682) draws attention to the fact that ABO-incompatible foetal cells, even if rapidly destroyed, should still be capable of stimulating Rh antibodies, as the products of the cell destruction will enter the maternal reticulo-endothelial system and will not just "go up in smoke." There is, however, a very considerable body of evidence to show that Rh-antibody formation is not in fact stimulated by such ABO-heterospecific pregnancies. One explanation of this anomaly is that the foetal cells are rapidly removed to phagocytic cells which break down the antigens before they have time to sensitize the antibody-producing tissue. On the other hand, a dosage effect may be involved—one large dose of antigen being less effective in sensitizing than repeated small doses. It is therefore reasonable to postulate that if foetal cells can be rapidly destroyed on entering the maternal circulation, then sensitization will not occur. If we can effect this and antibodies do not develop, there will be support for this hypothesis. On the other hand, if antibodies develop in spite of rapid elimination, the whole mechanism by which ABO-incompatibility protects will have to be reviewed.

We do not know if Race and Sanger[1] had any particular mechanism in mind when they used the word "elimination," but we use it without any specific connotation, not necessarily meaning haemolysis, as we do not know precisely how foetal cells are removed from the maternal circulation by different kinds of antibodies.

Dr. Marsh is no doubt aware that steroids have been used extensively with a view to protecting the baby in sensitized mothers, but according to Wiener[2] they are not effective. Whether or not these compounds would prevent initial Rh-sensitization is another matter, but we very much doubt whether even very large doses of steroids would induce a "total immunological paralysis," and the widespread use of massive steroid doses would entail a considerable degree of risk to the mother.

We entirely agree that it would be unwise and probably ineffective to inject incomplete antibodies into pregnant women, but what we suggested in the paper was that it *might* be helpful to give anti-D *after* the birth of the child to those women in whom transplacental haemorrhage of some size had been demonstrated.—We are, etc.,

RONALD FINN.
C. A. CLARKE.
D. LEHANE.
R. B. MCCONNELL.
P. M. SHEPPARD.

Department of Medicine, The University, Liverpool 3.

REFERENCES

[1] Race, R. R., and Sanger, R., *Blood Groups in Man*, 3rd edition, 1958, p. 315. Blackwell, Oxford.
[2] Wiener, A. S., *J. Amer. med. Ass.*, 1954, **155**, 63.

## Cortical Mastoidectomy

SIR,—With reference to the article by Mr. R. S. McAlary entitled "Cortical Mastoidectomy is Still Necessary" (June 24, p. 1802), I object to the diagnosis of acute mastoiditis in some of the cases presented—namely, 5, 6, 7, 8, 9, and 12. These "failed antibiotic" cases had only a persistent aural discharge from which sensitive organisms were isolated. I have time and again admitted young patients similarly treated with oral penicillin, and achieved dry ears and normal hearing with parenteral penicillin and attention to the upper respiratory tracts where the cause is often found. From a pathological standpoint, mastoid air-cells are often involved in the course of an acute otitis media, but as long as infection is confined to the lining membrane, even to the extent of forming granulations, we do not speak of mastoiditis because the process is still reversible. Mastoiditis means bone necrosis.

Mr. McAlary's description of some of his cases and criteria to operate is at times confusing. I am singling out: (1) The acute flare-up of a chronic otitis media followed by a brain abscess. Was the disease of the attico-antral type, in which case a form of radical mastoidectomy and not a cortical one should have been done? (2) The mastoid which became reinfected after operation suggests that a timely adenoidectomy would have been more adequate. On these grounds I think Mr. McAlary's paper fails to make a case for more frequent cortical mastoidectomies.—I am, etc.,

S. SILBERMANN.

Peace Memorial Hospital, Watford, Herts.

## Geographical Pathology

SIR,—Dr. Richard W. Payne's paper on "Pernicious Anaemia and Gastric Cancer in England and Wales" (June 24, p. 1807) was of interest to me as I was recently stimulated into making a similar inquiry regarding post-cricoid carcinoma. I have come across several patients with pernicious anaemia who developed post-cricoid cancer from two to fifteen years after their anaemia had been diagnosed, and the possibility arises of an association between the two conditions.

Since 1957 the Registrar-General has coded post-cricoid carcinoma as a distinct cause of death, and with the aid of figures he has kindly provided it has been possible to determine the mortality from this condition

in each region of the country for the years 1957–9. Post-cricoid carcinoma is primarily a disease of women, and indeed some authorities doubt whether it occurs in men except as an occasional rarity. In view of this

Post-cricoid carcinoma in women. Comparative mortality (%).

only the mortality in women is considered. The comparative mortality figures for women calculated in the same manner as Dr. Payne's give the following results:

| *Region* | *Comparative Mortality for Women* (%) |
|---|---|
| Northern | 94 |
| E. and W. Ridings | 100 |
| North-western | 114 |
| North Midland | 100 |
| Midland | 73 |
| Eastern | 79 |
| London and South-east | 81 |
| Southern | 67 |
| South-western | 116 |
| Wales | 240 |

The high incidence in Wales is most striking and the regional variation as a whole has some similarities to the variations found in the case of pernicious anaemia and gastric carcinoma. This is best illustrated by the map. The main difference is the low comparative mortality in the Midland region.—I am, etc.,

Department of Pathology,
St. Mary's Hospital,
London W.2.

A. JACOBS.

## Accident Neurosis

SIR,—Like Mr. J. A. Ryan (April 29, p. 1251), I also want to thank Dr. Henry Miller for his discussion of some of the effects of trauma. But I am sorry he has not given me an infallible means of distinguishing neurosis from organic post-concussional syndrome.

In one place Dr. Miller said a third of patients with minor head injuries developed neurosis. But he restricted his detailed study to only 47 with "gross and unequivocally psychoneurotic complaints." The chief distinguishing feature of these was that they returned to work after a lump-sum settlement. This is impossible to foretell, and therefore the diagnosis in such cases can only be retrospective. So far as I know, nobody has followed up a large series of such cases since H. E. Griffiths[1] denounced the "pest of the lump sum settlement." In those days it usually left the worker destitute after a few months. Griffiths cited Norcross, of New York, who in 1936 reviewed 321 patients three years after settlement of lump-sum claims. Of 67 patients classed as neurotic, 45 were back at work with weekly earnings much decreased, in 22 by more than 60%.

It is a grave error to generalize from the patients we dislike, and lay suspicion of dishonesty on every patient who fails to recover from an injury. More realistic is the committee of twelve surgeons headed by G. C. Manning,[2] who after four years' inquiry said the only one competent to judge the patient's fitness for manual work was the patient himself. Manning said it was unfair that medicine, whose only purpose is the relief of suffering, should be thus side-tracked by the courts and asked for opinions it is not competent to give.—I am, etc.,

East Melbourne C.2,
Victoria, Australia.

MICHAEL KELLY.

REFERENCES

Griffiths, H. E., *Proc. roy. Soc. Med.*, 1942, **35**, 502.
Manning, G. C., *J. int. Coll. Surg.*, 1960, **33**, 471.

## Connubial Diabetes and the Possible Role of "Oral Diabetogens"

SIR,—Dr. G. D. Campbell (May 27, p. 1538) presents some interesting speculations on possible reasons for a high incidence of diabetes in the spouses of diabetes patients at the diabetic clinic of the King Edward VIII Hospital in Durban, but the evidence he adduces for the existence of a high incidence of connubial diabetes seems to be deficient.

Dr. Campbell states that 8.8% is probably a low estimate of the incidence of diabetes in Natal Indians over 30. I don't know how many of the 1,900 of these people in the sample were over 30 and had spouses, but, if they all were and did, then the 1,900 spouses should include at least 167 diabetics (omitting a small correction for spouses initially known to be diabetic). Since only 61 diabetics were found among the spouses of diabetics, one may conclude that only about 36 or 37% of the diabetics had spouses. Only if a substantially smaller percentage than this were married would 61 be an unexpectedly large number of pairs of connubial diabetics in this sample. As for the "simultaneous emergence of the disease in these connubial pairs," is it not likely that a number of people might be stimulated to investigate the possibility of their suffering from diabetes by the diagnosis of diabetes in their spouses?—I am, etc.,

Central Research Division,
Becton, Dickinson and Co.,
Englewood Cliffs, N.J., U.S.A.

MARSHALL E. DEUTSCH.

## Acute Diabetic Abdomen

SIR,—I would like to make a further addition to the very useful list of medical causes of acute abdominal pain, besides diabetes, made by Dr. A. K. Chatterjee (May 27, p. 1539): it is very rarely pointed out in textbooks of surgery and medicine that organic disease or functional impairment of endocrine glands (chiefly the hypophysis, parathyroids, and adrenals) may present as an acute abdomen. I think it is very important to

bear in mind this possibility in view of the many cases in the literature in which useless surgical operations have been performed, even several times in the same patient, before the correct diagnosis has been established. The bibliography on this subject is summarized in a review I published three years ago.[1]—I am, etc.,

Medical Clinic,
University of Bologna, Italy. R. PELLEGRINI.

REFERENCE

[1] Pellegrini, R., *Endocr. Sci. Cost.*, 1958, **25**, 107.

## Dangers of Raw Milk

SIR,—The article by Drs. J. M. Black and I. B. Sutherland (June 17, p. 1732) is one of many which prove that the time has come to have all cows' milk made safe by pasteurization or boiling before ingestion by the human baby or by those of more advanced years who apparently believe that milk is a good food. It is well known—by the medical profession—that the consumption of a raw "foreign" milk may, and does, directly cause, or aggravate, certain conditions—for example, skin rashes and other allergies, ulcerative colitis, and brucellosis.

Why are the terms "T.T. Milk," "T.T. Dairies," and even "T.T. Farmers" so often used? Only the cow is attested. There are many channels through which tuberculosis (by a tuberculous herdsman or handler, as I know has occurred) and other diseases may be, and still are, conveyed from cow to the consumer. All can be prevented by adequate pasteurization of milk and ensuring that the human handlers have some instruction in hygiene.—I am, etc.,

Dundee. F. R. BROWN.

## Mortality from Primary Bone Tumours

SIR,—The extensive analysis of the mortality from primary bone tumours carried out by Drs. Alan Mackenzie, W. M. Court Brown, R. Doll, and H. A. Sissons (June 24, p. 1782), whilst an admirable statistical exercise, would seem in its present form to be of limited value. Despite the clearly stated caution in making deductions of tumour incidence, nevertheless it is suggested that reliable comparisons may be drawn in respect of "the impact of the various types of tumour in men and in women at different ages." Moreover, a tentative comparison has already been made with the radioactivity of water supplies.[1] It is difficult to see any value in these mortality data save for comparison with others derived from a similar compendious survey made elsewhere or for some other time span.

The age and sex distribution figures are clearly largely influenced by the major group of tumours included (osteogenic sarcoma), but the presence of significant numbers of other primary bone neoplasms of differing aetiology suffices to diminish the value of the data presented. Moreover, the total number of histologically verified osteogenic sarcomata collected during the three-year period 1951–3 would seem to be unduly small, even allowing for a recovery rate of 15%.

I have personally studied all cases of confirmed osteogenic sarcoma which could be traced for the years 1946–58 inclusive in the northern section of the South-west Hospital Board region (1951 population: 1.56 million). Eighty-seven such tumours were traced and showed a fairly steady annual incidence for this period. Since there is no reason to suppose that there is any marked geographical variation in their frequency, it may be estimated that the annual incidence of this tumour among the whole population of England and Wales would be of the order of 190 at least. The discrepancy between this estimate and the number of osteogenic sarcomata collected by Dr. Mackenzie and his colleagues may furnish an index of the cumulative effect of the many difficulties which beset this type of work.

Thus one wonders whether the mortality survey would not have been more valuable had it been restricted solely to verified cases of osteogenic sarcoma, extending the time span to yield a sufficiency of material for analysis. Had the final number of tumours still been modest, it would at least have been histologically homogeneous. This argument would seem to be all the more valid, since a declared purpose of the investigation was to review bone tumour mortality data in the light of possible connexion with radioactive contamination, and the majority of malignant tumours produced in bone by ionizing radiations have been members of the osteogenic series.—I am, etc.,

Bristol Bone Tumour Register,
Bristol Royal Hospital,
Bristol 1. C. H. G. PRICE.

REFERENCE

[1] Turner, R. C., Radley, J. M., and Mayneord, W. V., *Nature (Lond.)*, 1961, **189**, 348.

## Noise in Hospital

SIR,—Mr. Enoch Powell, Minister of Health, has told of a visit which he recently paid to a maternity hospital.[1] Rightly decrying the occurrence of noise in hospitals anywhere, he thought fit, however, to generalize with this averment: "Doctors are not always the most innocent" (that is, as producers of unnecessary noise). There followed then a reference to the presence of steel tips on the footwear of an accompanying consultant.

The Minister is correct in denouncing the all-too-prevalent racket within the buildings, especially that having to be endured by patients and night staff alike in the early hours of the morning. However, Mr. Powell's illustrations of its genesis are wide off the mark; the examples of noise-production such as he cites must surely be of the very greatest rarity. In a lifetime's acquaintanceship with hospitals, at home and abroad, I cannot recall having once heard a noisy tread from a member of the medical staff disturb a ward. When the Minister speaks of a "slamming door" being a crime he really is pillorying his own Ministry for countenancing the archaic structures in a hospital within the National Health Service which would permit a hospital door's capability of being slammed.

One prolific source of noise is always from the transport of garbage bins, milk cans, dispensary baskets, and the like when, arms on armour clashing, as it were, the busy and vocal porters are wont to bray down the resounding lift-shafts, "Hurry up below there and close them bloomin' gates!" Crash is what follows next when the steel gates are slammed. A Swiss inscription reads: *Sprechen ist silbern, Schweigen ist golden.* A mandate of this nature could well be the exordium to the employment of all early-morning ward maids. The golden qualities of silence rather than the chatterbox exchange of girlish confidences anent the previous evening's *divertissement* could, with advantage, be enjoined.

The Minister would also be well in favour with even steel-shod consultants if he were to see that the pro-

jected, stereotyped architecture for the national hospital building programme was of such design that no emergency admission could, in any way, disturb the occupants of a ward already composed for the night.

The Minister, finally, would indeed be canonized, earning a veritable halo on earth, if the ukase were promulgated from his headquarters that no drunk casualty case was ever to be housed in a bed within earshot of a decent, ailing citizen—or child.—I am, etc.,

Grimsby, Lincolnshire. DANIEL LAMONT.

REFERENCE

[1] *The Times*, June 12.

### Oral Contraception

SIR,—The letter by Dr. T. Lovegrove (June 24, p. 1830) implies that oestrogens are used for the suppression of ovulation in humans "in quantities large enough to cause a general hormonal upset," and suggests that it is "unwise to use them for contraceptive purposes" at present, mentioning their effects on cattle to support this view.

This does less than full justice to the vital facts already known about oral contraception. First, inhibition of ovulation is usually produced by a progesterone type of drug, and the amount of oestrogen supplement, whose withdrawal effect promotes the anovular menstruation, is small (0.075 mg. ethinyl-oestradiol, for example), less in fact than the usual therapeutic dose given for gynaecological disorders. Furthermore, it is taken intermittently, not continuously. Secondly, results of clinical trials throughout the world, but especially in Puerto Rico, the United States, India, Japan, and Great Britain, have not, so far, given any cause for alarm because of either immediate or remote dangers following their use.

It would indeed be a retrograde step if tacit acceptance of the present only "fairly effective" methods of family planning as an ideal were to discourage further clinical trials and research directed towards the discovery of the perfect birth-control pill. In fact, recent developments, shortly to be published, show that in the right circumstances the oral method compares favourably with existing conventional methods not only as regards efficacy and acceptability but also safety.—I am, etc.,

Bournemouth, Hants. GABRIEL V. JAFFÉ.

### Pep Pill Merry-go-round

SIR,—Of course it may not be a new syndrome, but I have now become aware of a merry-go-round which has for some time been before my unperceiving eyes. I refer to the exhibition—a curious medical use of the word—of slimming tablets. To reduce overweight is undoubtedly laudable whilst it lasts, which is perhaps for a month or so, but the above-mentioned exhibition very often continues unabated for month after month after month when the pretence of losing weight is only an excuse for something sinister.

The syndrome becomes established when the pep pills of the day are succeeded by the sedation of the night. Pep pills, sedation, more pep pills, more sedation: it is quite simple really. This may have good results, but the results as evidenced by the police court reports can be startling. To the ageing, their aphrodisiac effects can be encouraging: the old man's pop songs.

Maybe it is pusillanimous to discourage anything which illuminates the highlights of a sometimes sombre world. It may be good medicine, I don't know; but, at least, we are all entitled to prescribe the drugs which our patients demand. Yes, "demand" is the right word: try taking them off them. It might perhaps be better medicine and better for our self-respect if we analysed the true nature of our treatment. I wonder what the word treatment sometimes means.—I am, etc.,

Topsham, Devon. F. E. GRAHAM-BONNALIE.

### Prevention of Dental Caries

SIR,—In reply to Dr. R. A. Holman (June 3, p. 1608) he neglected to mention that the work of Hein *et al.*,[1] to the effect that sodium fluoride is more toxic than cryolite, related to the 24 hour intraperitoneal toxicity which has no bearing on the behaviour of such compounds when consumed by mouth at a concentration (of fluorine) of 1 part per million of water. As regards Nesin's[2] criticism of the work of Hagan *et al.*,[3] it would have been more helpful if it had been mentioned that Dr. Nesin is, or was, "Director of Laboratories, Department of Water Supply, Gas, and Electricity, City of New York." Readers would then have been able to decide whether to accept his opinion or that of the various public health and other authorities who appear to have found a considerable measure of assurance in the data produced by Hagan *et al.* An important part of these data consisted of a comparison of 32 pairs of "fluoride" and "non-fluoride" cities in the United States of America, and the adjusted mortality rates for cancer in the two groups were, respectively, 135.4 and 139.1 per 1,000 of the population. Incidentally, when Dr. Holman mentions 16 years as the limit of experience of the ingestion of fluoride from water supplies he is evading the point made in my previous letter, namely, that we have valuable evidence from observations conducted in areas in this country which have always had a high content of fluorine from natural sources.—I am, etc.,

London W.C.1. A. J. DALZELL-WARD,
Medical Director,
Central Council for Health Education.

REFERENCES

[1] Hein, J. W., *et al.*, *J. dent. Res.*, 1951, **30**, 466.
[2] Nesin, B. C., *J. Maine Water Utilities Assoc.*, 1956, March 10.
[3] Hagan, T. L., Pasternack, M., and Scholz, G. C., *Publ. Hlth Rep. (Wash.)*, 1954, **69**, 450.

*** This correspondence is now closed.—ED., *B.M.J.*

### Collapse from Reserpine

SIR,—As Dr. Denis F. Hawkins points out (May 20, p. 1465), clinical experience in stable hypertensive patients has shown that the effects of reserpine are cumulative. Unfortunately, hypertension in toxaemia is not stable and tends also to be cumulative, so that, when the "given effect" required is control of blood pressure in toxaemia, it is not possible to maintain control with "great" reductions in dose of reserpine; increased dosage may be required.

Dr. Hawkins can see no obvious reason why reserpine treatment (with or without bed-rest) should not be changed (to rest and sedatives) at 36 weeks' maturity or even earlier in pregnancy (i.e., when the period of maximum danger is approaching). If reserpine were required earlier and stopped at this stage, many otherwise avoidable inductions of labour would, despite bed-rest, become necessary. Inductions are not devoid of

danger, and they may even have to be followed by caesarean-section rescue operations.

The drawbacks and disadvantages of bed-rest are little appreciated by those lacking experience in general practice; nor are the advantages of treating early toxaemia with reserpine apparent to those who have not considered them. Not the least of these is the fact that the average cost of providing a bed in a British maternity hospital, for one week, would pay for enough reserpine tablets to treat 560 ambulant patients, suffering from mild toxaemia, for a week. From time immemorial rest has been the approved basis of treatment for toxaemia, whether mild or severe; toxaemia has nevertheless become the leading cause of maternal mortality in Britain, and is one of the principal causes of our static perinatal mortality. The efficacy of bed-rest is not particularly evident in these facts. The primary objective for conquering toxaemia is to secure early diagnosis and prompt treatment. I believe that will never be attained by ordering treatment for early, mild toxaemia that is inconvenient, and unacceptable to many mothers when they feel perfectly well, or who tend to be uncooperative or over-conscientious.

The danger of collapse in labour following reserpine is largely theoretical, and negligible when compared with the danger of toxaemia, both in pregnancy and in labour, to mother and baby. If this danger can be minimized by reserpine, the drug should be given in the most effective manner—i.e., continued until term.—I am, etc.,

Reading, Berks. K. D. SALZMANN.

REFERENCE

[1] Salzmann, K. D., *The Aetiology and Arrest of Pre-eclamptic Toxaemia*, 1960, p. 54. H. K. Lewis, London.

## "Albustix" Test

SIR,—During the 1960 medical examinations of new university entrants, urine specimens from 837 men and 254 women students were tested for protein by "albustix" reagent strips. Positive reactions were obtained for 58 (6.9%) men and for 30 (11.8%) women. These differences are significant ($0.05>P>0.02$). The 88 positive reactors were recalled to test the validity of the results by boiling and acidifying the urine. Of 45 (77.6%) men and 16 (53.3%) women who co-operated, proteinuria was confirmed in only one woman.

A sample of 120 (90 men, 30 women) was chosen at random from the new university entrants. In this sample four men and four women showed positive reactions to the albustix test. A scrutiny of the previous medical histories showed that only one man in the sample had a previous history of renal disease, and his urine was negative to the albustix test. From this sample urine specimens were obtained from 39 men and 15 women whose urines were negative to the albustix test. These urines were also tested by boiling and acidifying; the absence of protein was confirmed in each specimen.

When compared with the usual test for the presence of protein in the urine, or with the possibility of renal disease as judged by the previous history, albustix reagent strips give many false positive results, more frequently in women than in men. They do not, however, appear to give any false negative results. The test is simple and speedy and is a useful screening technique.

I thank the staff of the Student Health Department, particularly Sister Aspdin, for help in this small survey.

—I am, etc.,

Department of Student Health,
The University,
Leeds 2. S. E. FINLAY.

## Second Ectopic Pregnancy

SIR,—I was very interested in the case of a bilateral ectopic pregnancy reported by Dr. A. H. Bartley (April 29, p. 1252). I would like to report the following three cases and to mention some views of the causation of this abnormality in some women.

*Case 1.*—Married in 1943 at the age of 27. She was sterile for five years, and was a very tense and anxious person. She very much wanted to have a child. After nine weeks of amenorrhoea she had a ruptured ectopic pregnancy of the right Fallopian tube in September, 1948. A similar thing happened in December, 1950, on the left side, after two and a half months of amenorrhoea. In both cases salpingectomy was performed.

*Case 2.*—Age 20. A very tense and anxious person having a great deal of emotional difficulties since childhood. She was sterile for three years and very much wanted a child. On March 8, 1956, after nine weeks of amenorrhoea, she had a ruptured ectopic pregnancy of the left Fallopian tube, and on December 3, 1957, after eight weeks of amenorrhoea there was a right ectopic pregnancy which ruptured. Bilateral salpingectomy was performed.

*Case 3.*—Age 21. Tense, anxious, and emotionally unstable. She had a ruptured left tubal pregnancy in 1953 after eight weeks of amenorrhoea. Salpingectomy was performed. A right tubal pregnancy was diagnosed in 1960 and at the operation it was found that the ectopic mole was adherent to the bowel and uterus.

All these patients were tense and anxious. There is little doubt that their sterility was of psychogenic origin. It is well-known that psychosomatic conditions affecting some parts of the body may be brought about by a spasm of the smooth muscle as a result of psychological conflicts. It would seem likely that a similar spasm of the Fallopian tubes is the cause of psychogenic sterility. If an ovum is arrested during its migration through the tubes by such a spasm, tubal pregnancy may be the result. The intensity of the spasm may vary with the amount of anxiety and tension of the individual.

Stallworthy[1] demonstrated that tubal spasm may be emotional in origin. Kroger and Freed[2] discussed the role that emotions play in the production of tubal spasm, which is often responsible for psychogenic sterility. Sandler[3] described a case of a woman, aged 24, who was very tense and nervous. At the insufflation of the Fallopian tubes there was apparent occlusion and no peristalsis at 200 mm. of mercury. She was nervous during that investigation and so her attention was distracted by making a joke; she immediately burst into laughter. As she laughed the needle dropped to 40 mm. and the gas passed with peristalsis. Gynaecologists are well aware that tubal occlusion is difficult to diagnose in nervous individuals and have found that tubal insufflation is best performed under thiopentone sodium or hypnosis, since in this state the nervous stimuli are minimal.

The fact that many women who have long been sterile conceive within a short time of adopting a child is very strong evidence of functional causation of that sterility. The following case may be of interest, as it shows how anxiety and tension may cause psychogenic sterility and ectopic pregnancy.

The patient was of German stock and was married in 1952 at the age of 26. She was a very tense and anxious subject and emotionally unstable. She attended in 1957 an infertility clinic, and the investigations carried out there showed that the Fallopian tubes were not patent and that she did not ovulate. She was seen in April, 1958, when she was in a very depressed and anxious state because of her sterility, as she very much desired to have a child. It was explained to her that the likely cause of her sterility was her inability to relax due to her tension and anxiety, and if these were relieved there might be a chance for her to conceive. She did not accept that offer, and preferred, instead, to have further investigations carried out in another hospital. Endometrial biopsy performed there showed that she did ovulate, and she was advised to limit intercourse to the intermenstrual period between the 12th and 20th day. On May 5, 1960, she suddenly developed very severe lower abdominal pains with tenderness and vomiting; she was very shocked. She had had amenorrhoea for seven weeks. She was admitted into hospital, and laparotomy performed there showed a ruptured left tubal pregnancy with approximately three to four pints of blood in the peritoneal cavity. Left salpingectomy was performed. On October 8, 1960, she became disorientated, hysterical, and very violent after her return from a visit to Germany, where she had a severe domestic upset. She was treated in hospital for a few days as a case of hysterical dissociation with depressive features. This last event proves well the emotional instability of the patient, which was an important factor in her tension.

—I am, etc.,

London S.E.25. A. FRY.

REFERENCES


1 Stallworthy, J. *J. Obstet. Gynaec. Brit. Emp.*, 1948, **55**, 171.
2 Kroger, W. S., and Freed, S. C., *Amer. J. Obstet. and Gynec.*, 1950., **59**, 867.
3 Sandler, B., *Practitioner*, 1960, **184**, 355.


## Aplastic Anaemia due to Potassium Perchlorate

SIR,—You may think that the dangers of potassium perchlorate therapy have been sufficiently emphasized in your recent medical memoranda (May 13, pp. 1368 and 1369) and leading article (May 27, p. 1520), but if you believe that further cases should still be made known as rapidly as possible, here follow details of another.

In 1957 a female patient of 35 was diagnosed as suffering from thyrotoxicosis, confirmed by radioactive iodine neck-to-thigh ratio test (dosage 10 $\mu$c). She was treated with methyl thiouracil, having a good response; this was continued for 18 months, when she was euthyroid and the thiouracil was stopped. Sixteen months later she again showed signs of thyroid over-activity, with loss of 12 lb. (5.4 kg.) in weight, recurrence of bruit over the thyroid, a raised B.M.R., etc.; a further radioactive iodine test was not done. In the following month she was given potassium perchlorate tablets 200 mg. q.d.s., which were increased after two months to 400 mg. t.d.s., being reduced after two further months to 200 mg. t.d.s. Six months later pallor was noted; a haemoglobin of 64% was found, and iron therapy begun, but despite this within a month the haemoglobin had fallen to 46%. She was readmitted to hospital, where the sternal marrow was reported as showing a general hypoplasia with the red cells relatively more affected, a normal amount of free iron being present. The potassium perchlorate was immediately stopped. Further blood counts at various times showed a continuously low haemoglobin, white cell counts below 3,000, and 50,000 platelets, reticulocytes varying between 0.9 and 2%.

The presumptive diagnosis is aplastic anaemia due to potassium perchlorate therapy, though at the moment there are hopeful signs of a recovering bone marrow.—I am, etc.,

Aston Clinton, Bucks. V. E. LLOYD HART.

## Functional Efficiency of Circle of Willis

SIR,—On March 25 (p. 858) Dr. C. J. Dickinson published a paper entitled "Functional Efficiency of the Circle of Willis." The perfusion method he used has been criticized by Dr. Robert Lowe in a letter (April 15, p. 1109). I would like to add another point, which seems to me to cast serious doubts on Dr. Dickinson's conclusions. He has used both ischaemic and haemorrhagic lesions among his cases without stating their exact relationship. It could be argued that narrowing of a carotid artery prevents rather than enhances the possibility of a haemorrhage on the same side. If this were true, it would explain Dr. Dickinson's results, assuming about an equal number of ischaemic and haemorrhagic lesions among his 31 cases.—I am, etc.,

Medizinische Universitätsklinik, Bürgerspital, Basel, Switzerland. E. STRICKER.

## Drugs in Parkinsonism

SIR,—I read with interest the article by Drs. P. R. Uldall and John N. Walton and Mr. D. J. Newell on chlorphenoxamine hydrochloride in Parkinsonism (June 10, p. 1649).

My experiences with this drug do not agree with those described by these authors. I first obtained a supply of chlorphenoxamine hydrochloride from Germany under the trade name of "systral," for a pilot clinical trial to assess its value on the treatment of all forms of Parkinsonism. After systral was distributed in this country as "clorevan" I completed the trial with these tablets, and gave them to 30 patients suffering from all forms of Parkinson's disease taken at random from over 400 patients attending my Research Parkinson's Clinic regularly. 50 to 100 mg. three times a day was prescribed. Ten patients were given the drug by itself, whilst in the remainder it was added to their usual drug or combination of drugs.

The drug had no beneficial action in the first group and only three patients in the other groups thought they had derived a little benefit. There are a number of reasons why this discrepancy should exist. Foremost is the totally inadequate number of patients included in the trial. The double blind technique is rendered useless by the normal variation in the symptoms of Parkinson's disease. For these and other reasons an alternative method for the evaluation of drugs in the trial of Parkinson's disease was described.[1]—I am, etc.,

Dudley Road Hospital, Birmingham 18. R. O. GILLHESPY.

REFERENCE


1 Gillhespy, R. O., and Ratcliffe, A. H., *Brit. med. J.*, 1955, **2**, 352.


## Leg Ulcers

SIR,—I trust that even at this belated date (due to distance) you will permit me to comment on the article by Drs. A. Girdwood Fergusson and James C. P. Logan (March 25, p. 871). My remarks are confined to the 96% of ulcers classified as gravitational or "varicose." It has long been recognized that topical applications to ulcers have little if any influence (except occasionally harmful) on healing of these ulcers, and to believe that they do is to ignore basic pathological physiology. Varicose ulcers occur and persist because of oedema of the parts consequent upon raised venous pressure from whatever cause. Control the oedema and the ulcer will

inevitably heal—irrespective of what it is dressed with. To keep the ulcer healed all one needs to do is to control the oedema either by dealing with its cause, if amenable, or by effective compression of the leg.

I have almost never had to put a patient to bed to heal his ulcer (in any case, unless he lies recumbent with the foot of the bed elevated, the venous pressure in the legs is still raised) but have used one-way stretch compression bandaging, together with active ambulation[1]—a physiological approach—to achieve consistently excellent results and without the use of expensive and scarce in-patient treatment and facilities. (The average cost of bandage and dressings is about £A.1=16s. sterling.)—I am, etc.,

Melbourne, Australia. W. STERN.

REFERENCE

[1] Stern, W., *Med. J. Aust.*, 1960, **2**, 292.

SIR,—Dr. Allan Bigham's letter (May 6, p. 1323) about the obese elderly patient suffering from leg ulcers, with oedema, prompts me to write and let you know that I have had considerable success with these cases by using small doses of the newer oral diuretics in conjunction with an antibiotic. Swollen oedematous legs and infection seem to subside if a simple non-irritating dressing with a firm supportive bandage is applied to the affected leg.—I am, etc.,

Bulawayo, S. Rhodesia. H. J. KINGSLEY.

### Vaccine Storage

SIR,—Dr. M. J. Derbyshire's letter (June 24, p. 1833) under the above heading interested me, as I am one of those "doctors with surgeries away from their domestic refrigerator."

I have been using his technique for some years, with one slight but very convenient modification. Our large, wide-mouthed thermos flask would appear to be the same, but, instead of plastic bags of ice, I use those neat screw-top plastic bottles our drug firms so generously send us to spray our noses with "this and that," *almost* fill them with water, and keep them in my refrigerator under the ice compartment. They are thus always ready for use. They will not damage the flask.—I am, etc.,

Wallington, Surrey. C. R. NUNAN.

SIR,—The thermos flask method of cold storage, described by Dr. M. J. Derbyshire (June 24, p. 1833), has its uses, but also its dangers. If the preparations to be stored are viral vaccines (poliomyelitis, smallpox, and yellow fever), the method is relatively safe, provided the ice is replenished as soon as it has disappeared: the danger with such vaccines is a rise of temperature above 10° C., which will cause loss of potency, especially of the rather susceptible yellow fever vaccine.

With other biological preparations, such as antisera and vaccines (including toxoids), the danger is that of freezing. Storage of these products at or below freezing point is harmful: deterioration of a product which is frozen solid may be rapid. In many vaccines a granularity develops and the associated destruction of antigenicity is probably due to local increase in salt and preservative concentration during freezing and thawing.

This is not to decry the thermos flask method, which, properly used, is a good one. When using it, however, it is necessary to be fully aware of the latent dangers of deterioration of biological preparations.—I am, etc.,

The Wellcome Research Laboratories, Beckenham, Kent. D. A. CANNON.

# Obituary

## F. G. HOBSON, D.S.O., D.M., F.R.C.P.

Dr. F. G. Hobson, honorary consulting physician to the United Oxford Hospitals, died on June 26 at the age of 69.

Frederick Greig Hobson, who was a member of an old Oxford family, came up to New College in 1910 from Westminster School to read medicine, but as soon as he had taken Schools the first world war broke out. Hobson, being the proud possessor of a motor-bicycle, at once volunteered as a dispatch rider and revealed all those attributes—courage, a selfless devotion to duty, and inexhaustible energy—which were to characterize his life. By 1917 he was a brigade major and had been awarded the D.S.O., the citation reading, "During thirty hours he continually organized parties for water and bomb carrying and also for carrying the wounded."

The precision and planning of things military appealed to him, but the attraction of medicine was stronger, and he had already come under the spell of Sir William Osler, then Regius Professor of Medicine. So a promising Army career was abandoned and Hobson completed his medical training at St. Thomas's Hospital, where, after graduating in 1919, he held house appointments. He then returned to Oxford, at first to carry out research work with Professor Georges Dreyer, as he had been awarded the Theodore Williams scholarship in pathology, but soon he set up in practice in St. Giles and rapidly built up a large private practice. He had married Audrey Gotch, the eldest daughter of Professor Francis Gotch, Wayneflete Professor of Physiology, and the perfect harmony of their married life was tragically broken by Mrs. Hobson's death in December, 1959.

In 1921 Dr. Hobson took the M.R.C.P. and in the following year was appointed assistant physician to the Radcliffe Infirmary, and until his retirement as senior physician in 1956 he devoted much of his energies to the work of the hospital. He was also physician to several of the surrounding hospitals—Wallingford, Savernake, and Marlborough—and to many schools. He was consultant to the Territorials and served on innumerable boards and committees. He took a full part in Oxford medical life, in the B.M.A. (he was a past-chairman of the Oxford Division, a past-president of the Berks, Bucks, and Oxford Branch, and a vice-president of the Section of Medicine at the Annual Meeting in 1937), Oxford Medical Society, Circle of Willis, and Medical Club, and was popular as a lecturer. In the University of Oxford he held the Litchfield clinical lectureship in medicine and was an examiner. He proceeded to the degree of D.M. in 1923 and was elected F.R.C.P. in 1933.

In 1936 the British Medical Association held its 104th Annual Meeting in Oxford, under the Presidency of the Regius Professor, Sir Farquhar Buzzard. Dr. Hobson, as local general secretary, revealed his remarkable gift for organization, for with seemingly effortless ease he created one of the most successful meetings on record. It was at this meeting that Sir Farquhar Buzzard selected as the title of his Presidential address "And the Future," in which he spoke of an ambitious dream of developing a postgraduate medical school at Oxford integrated with the scientific departments, and it was then that Lord Nuffield took the first step in turning the dream into a reality by the benefaction which he gave to the University in October of the same year. It was inevitable that the medical staff of the Radcliffe Infirmary should view with some concern the grafting on to their county and city hospital of a galaxy of high-powered professorial departments, and it was Hobson, as honorary secretary of the medical staff committee, who played a large part in assuaging their anxieties and ensuring that the Radcliffe Infirmary in its transformation to an internationally

famous school of teaching and research, never lost its sense of responsibility for the patients of the district.

A colleague writes: Dr. Hobson was a general physician, with a special interest in cardiology, and both as a consultant and a teacher it was his thoroughness and attention to detail and to the fundamentals of medicine that made him outstanding; nothing was too much trouble, no detail of care was too trivial to be considered scrupulously. His humanity was great, and he knew his patients as his friends and remembered them as friends whom he would help in their troubles to the utmost of his ability. General practitioners appreciated his sound diagnostic skill, but in addition he was especially popular because he himself had been in general practice and could see the problems of a case from their angle. He was generosity itself, and he and his wife were ever ready to assist students or colleagues, so that it would have been as appropriate at 20 St. Giles as it is at Lambaréné to see the inscription, "Here at whatever hour you come, you will find light and help and human kindness."

Fred Hobson was one of those rare individuals who are able, no matter how busy they are, to find time to undertake still more, and in the midst of his large private practice and heavy hospital duties he created the leisure to write a number of valuable papers, though writing was never easy for him; draft after draft would be prepared in his elegant script, until his friends convinced him that it could not be polished further. His first publication, while he was working with Professor Dreyer, was "A Comparative Study of Basal Metabolism in Normal Men," published in the *Quarterly Journal of Medicine* in 1923, and it is very typical of the man that there was an appendix which started, "The Benedict clinical calorimeter as supplied by the Sanborn Company shows poor workmanship in all its details and in certain respects its deficiencies render rapid and accurate working well-nigh impossible. . . ." The defects are then set out and the methods adopted to overcome them. There were a number of papers on infectious diseases—he was particularly interested in scarlet fever—and his monograph *Medical Practice in Residential Schools* (1938) is a classic. In more recent times his study of the hazards of teeth or fragments of teeth for patients with subacute bacterial endocarditis (published in the *B.M.J.* in 1956) is of considerable practical importance, and he was responsible for initiating and co-ordinating an excellent field investigation of glandular fever, published in this journal three years ago.

He played as hard as he worked—sailing, bird-watching, bee-keeping, gardening (preferably of the destructive and constructive variety), and carpentry, at which he was a real craftsman—these were his recreations at his Chichester Harbour cottage, and here he would relax energetically with his family. His son, Dr. Quentin Hobson, is consulting physician to the West Middlesex Hospital; his eldest daughter is married, and his younger daughter is a physiotherapist.

Shortly before his retirement Hobson suffered a severe and complicated myocardial infarct, from which he made a good recovery, but then he developed peripheral vascular ischaemia, which necessitated amputation of one leg, and so a man, whose pleasure was in activity and strenuous exercise, was cruelly restricted. He bore his hardships bravely, and was accepting that he must occupy himself at his desk, and try to bury the sorrow of his wife's death which was tearing away his heart, but it was very hard. One of his last writings was a delightful memoir of Sir William Osler (*Oxford Medical School Gazette*, 1961, **13**, 93) in which he recounted the influence that Osler had upon him as a medical student and young practitioner; writing of the impact of Revere's death on Osler, he said, "The sparkle of life had left him."

Dr. Hobson knew only one standard, the highest, and his devotion to the ideals of his profession will not be forgotten.

## MARCEL JUNOD, M.D., F.F.A. R.C.S.

Dr. Marcel Junod, a vigorous and courageous worker for the International Committee of the Red Cross during the past 25 years, died on June 16 in the Cantonal Hospital, Geneva, where he was director of the department of anaesthetics. He was 57 years of age.

Marcel Junod was born in Neuchâtel, and graduated in medicine in 1929. In 1935, when he was assistant director of the medical clinic at Mulhouse, he was asked by the International Committee of the Red Cross to go to Abyssinia and organize ambulance and other services for the care of wounded and prisoners of war during the Italo-Abyssinian war. Not long after his return from Africa he went to Spain during the civil war there as the delegate-general of the International Committee. During the second world war he led numerous missions to all the combatant countries, including Japan, and, in the best tradition of his country, carried out work of the utmost humanitarian importance, often risking his own life and subjecting himself to great physical hardships. He was one of the first Europeans to enter Hiroshima after the dropping of the atom bomb on that city. After the war he worked for a time for Unicef in China. Since 1952 he had been a member of the International Committee of the Red Cross, and last year he accompanied the president of the committee on an important mission to Warsaw and Moscow.

Dr. Junod's health had not been good for some time, and no doubt the hardships he suffered during the war exacerbated the circulatory disorder from which he suffered. It was because of this that he decided to specialize in anaesthetics, believing that it would require less physical activity than the other forms of practice. After studying at the Middlesex Hospital in London, he quickly became one of the leading anaesthetists in Switzerland and was elected a Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons of England in 1954.

Dr. Junod was much more than an idealist: by going and seeing things for himself and by patient and arduous negotiations he was successful in bringing relief and comfort to men and women of many nations in a war-torn world.

## LOUIS M. ORR, M.D.

Dr. Louis M. Orr, immediate past president of the American Medical Association and chairman of the A.M.A.'s Commission on the Cost of Medical Care, died suddenly at his home in Orlando, Florida, on May 23 at the age of 61. He was a specialist in urology and a founder member of the American Board of Urology.

Louis M. Orr was born on September 27, 1899, in Cumming, Georgia. He was educated at Emory University, Atlanta, and graduated M.D. from the medical school in 1924. He practised for a short time in Cleveland, Ohio, and then settled in 1927 in Orlando, where he was appointed chief of urology at the Orange Memorial Hospital. He became president of the South-eastern Section of the American Urological Association in 1943. He was also a member of the American Association of Genito-Urinary Surgeons, the International Urological Association, the American Board of Urology, and a Fellow of the American College of Surgeons. He served in the second world war as a colonel in the Medical Corps and commanded the 15th Hospital Center in Europe from 1943 to 1945.

Dr. Orr, who was 113th in line of succession of presidents of the A.M.A. when he was in office in 1959–60, was prominent in the affairs of his association. He was a former vice-speaker of its House of Delegates and an *ex-officio* member of its Council on Constitution and by-laws. He was also a member of the A.M.A.'s Council on Medical Services and its Federal Medical Services Committee. At the time of his death he was chairman

of the A.M.A.'s Commission on the Cost of Medical Care. A strong opponent of any system of Government medicine, during his year as president Dr. Orr travelled widely in carrying out one of the busiest speaking programmes ever attempted by an A.M.A. officer. He spoke in nearly every state, and in his official capacity he visited Canada, Brazil, the Far East, and Europe. He represented the A.M.A. at the installation of H.R.H. the Prince Philip, Duke of Edinburgh, as President of the B.M.A. in the Great Hall of B.M.A. House on October 28, 1959.

## GEORGE DALZIEL, *M.C.*, M.B., Ch.B., F.R.F.P.S.

Mr. George Dalziel, formerly surgeon in charge of wards at the Western Infirmary, Glasgow, died in Glasgow on June 24 at the age of 72.

George Dalziel was the elder son of the late Sir Kennedy Dalziel, whose skill in the teaching and practice of surgery is often recalled by an older generation of doctors. Educated at Glenalmond and Glasgow University, he graduated M.B., Ch.B. in 1912, and thereafter occupied resident posts in the Western Infirmary. In one of these he was house-surgeon in his father's wards, and a photograph of the two men taken during a ward visit is carefully preserved in the infirmary. During the first world war he served in France, Egypt, and Palestine, and in 1917 was awarded the Military Cross.

Immediately after the war, in 1919, three memorable appointments were made to the dispensary surgical staff of the Western Infirmary—Mr. J. Scouler Buchanan, Mr. Walter W. Galbraith, and Mr. George Dalziel—and for the next 35 years an increasing burden of surgical work was borne by this triumvirate—for triumvirate indeed it was. And now we mourn the passing of George Dalziel, the last survivor of that notable small group. In 1923 he became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow, and in 1940 he was appointed surgeon in charge of wards in his beloved Western Infirmary, which he served so well.

Clearly George Dalziel inherited the surgical abilities of his father, whom in many ways he resembled. To watch him operate was to see the confidence and swift dexterity of the born craftsman working in an atmosphere of serenity. Many visitors to his theatre gazed in awe and admiration at the ease and speed with which he accomplished his list of operations. To the many students who attended in earlier days his dispensary and later his wards, he was a delightful teacher whose example and precepts were followed throughout many medical careers.

Blessed in a happy and absorbing family life, George Dalziel found also a satisfying companionship in his golf, in shooting, in angling, and, since his retiral in 1954, a new interest in the care of his garden. In addition he found time to hold twice the office of Master of the Princess Masonic Lodge of Glasgow and to serve as deputy Provincial Master of Masons.

He is survived by his widow and two daughters, to whom his many friends and colleagues extend their deep sympathy. —H. J. P.

## A. H. CRAIG, M.B., Ch.B.

Brigadier A. H. Craig, formerly of the Indian Medical Service, died at Fleet on May 26. He was 68 years of age.

Alexander Henderson Craig entered the University of Aberdeen in 1911. As a member of the 4th Territorial Battalion of the Gordon Highlanders he was mobilized on August 4, 1914, and saw active service in France and Flanders before, in the autumn of 1915, he was sent back by the authorities to his medical studies. He graduated M.B., Ch.B. in 1916, and then served in Salonika, Russia, and Constantinople. He was demobilized in 1920, but after an interval was given a commission in the Indian Medical Service.

Craig remained on the military side during his entire service in the I.M.S., specializing for a time in radiology, but he was regarded as an outstanding military administrator and in 1937 was marked out by the award of a brevet lieutenant-colonelcy—the gateway to further high rank in military circles. The outbreak of the second world war found him as D.A.D.M.S. at Army Headquarters, India, where he was retained as an essential A.D.M.S. (personnel), coping with the ever-increasing demands of the Indian Army for medical staff. He succeeded in escaping to active service, but by 1942 the rule "too old at 45 for service with an active division" was in force and he finished the war in a succession of high administrative appointments in India as Inspector of Medical Services and as D.D.M.S. at G.H.Q.

In 1947 he had a severe coronary thrombosis from which he never fully recovered, and he lived quietly in retirement at Fleet. A conscientious military officer, capable of prolonged hard work, he was responsible for much of the back-room work which made the general military medical administration in Asia run smoothly. Our sympathy is extended to his wife and family.—G. R. McR.

## T. ROBERTSON, M.B., Ch.B.

By the death of Dr. T. Robertson on April 15 Sheffield has lost one of its foremost medical practitioners. He was 78 years of age.

Thomas Robertson received his medical education in Edinburgh, graduating M.B., Ch.B. in 1907. After qualifying he went to the Royal Hospital, Sheffield, where he held the posts of house-surgeon, ophthalmic house-surgeon, and house-physician to the late Sir Arthur Hall. He was then appointed R.M.O. at the Ecclesall Infirmary, Sheffield. After this extensive clinical experience he became a partner in a practice in Sheffield, remaining in it to the time of his death. He was at one time anaesthetist to the Royal Infirmary, and he became well known in the practice of this specialty throughout the West Riding of Yorkshire.

Robertson was a tall man of distinguished appearance and a great charm of manner which gave confidence to his patients. In his youth he had been a scratch golfer, and up to the last he was difficult to beat. He was a man of wide culture and his large library included Latin and Greek classics which he read in the original text. He held that they lost something when translated into English. He was the best type of general practitioner, and one cannot help feeling some sorrow that doctors of such broad general culture are so rarely produced to-day. He had a happy married life, and our sympathy goes out to his widow and daughter.—J. H. C.

## H. S. ANDERSON, C.M.G., L.R.C.P., L.R.C.S. L.R.F.P.S.

Lieutenant-Colonel H. S. Anderson died on May 24. He was 89 years of age.

Henry Stewart Anderson was born in 1872, the fourth son of the Rev. Samuel Anderson, of Dunmurry, Belfast. After education at St. Columba's College he embarked on a business career, but the call to medicine soon came in the guise of a man who bled to death because neither Anderson nor his companions had the simple medical knowledge necessary to save his life. From that day his course was clear—the saving of life and relief of suffering. He studied at Queen's College, Belfast (1894–8) and qualified in Edinburgh L.R.C.P., L.R.C.S., and Glasgow L.R.F.P.S. in 1898. He immediately joined the R.A.M.C. and was medical officer to the D.C.L.I. in South Africa.

After service in Burma and India, Anderson was in Malta at the time of the Messina earthquake and was largely responsible for the dispatch of a British relief party to the

scene. He had been reading about the landing of the Knights of Malta at Catona several centuries earlier, and saw the opportunity of following in their footsteps. His friend, H.R.H. the Duke of Connaught, was impressed by the idea and as C.-in-C. gave it powerful support. The Italian Government refused the first offer of help, but the Queen of Italy, after a visit to the scene, caused this decision to be changed. As a result a party of four R.A.M.C. doctors and two Q.A.I.M.N.S. sisters, together with British civilian doctors and nurses and other R.A.M.C. personnel, landed at Catona from H.M.S. *Duncan* on New Year's Day, 1909, four days after the disaster. An article by Anderson describing their work was published in the *Journal of the Royal Army Medical Corps* of March, 1909. He and the Commander of the party, Major G. S. Crawford, were made Officers of the Order of the Crown of Italy, and also received the Italian Red Cross and Messina medals.

In 1914 Anderson went with the 1st Battalion North Staffs to France, but was invalided home in 1915. Later in 1915 he was appointed senior M.O. of the *Britannic*, sister ship of the *Titanic*. He supervised the medical side of her fitting-out and sailed with her till she was sunk in 1916. In 1917–19 he commanded the military hospital installed in the Citadel at Cairo, and later the Palestine General Hospital at Ludd. He was awarded the C.M.G. in 1918. He retired in 1924, but remained with the Army until 1937 as M.O. to the depot in Northampton. He was keenly interested in the work of the Royal Life Saving Society, St. John Ambulance, and the Royal Geographic Society. He had been a member of the B.M.A. since 1904. He married in 1910 Cicely May Steele, and she and their only son survive him.

## S. C. J. SHORTMAN, M.B., Ch.B.

**Dr. S. C. J. Shortman died suddenly on May 27, at the age of 26.**

Stanley Clifford John Shortman entered the Faculty of Medicine of the University of Bristol in 1952. After a distinguished student career, he graduated with second-class honours in 1957 and was awarded the Gold Medal as the best student of his year. He held house appointments at the Bristol Royal Infirmary before joining the R.A.M.C. for his period of National Service, which he had almost completed when he died.

A. D. M. S. writes: To those of us who knew him well it was obvious that Stanley Shortman was destined to be a good doctor in whatever sphere of medicine he chose to make his mark. After a brilliant career as a student he joined the house-staff of his teaching hospital, and I became intimately associated with him in my capacity as R.M.O. The best way to get to know people really well is to live with them in the restricted confines of a hospital. It was a pleasure to be associated with Stanley Shortman under such conditions. At all times he was obsessed with the idea of doing his utmost for the patients in his charge. His personality was refreshingly honest and direct, and it will always be a tragedy that both ourselves and future patients will be denied his comments and help, supplemented by the wisdom of increased experience.

Our sympathy is extended to his wife and family in this time of deep personal loss.

## C. P. OLIVER, B.A., M.B., B.Ch.

**Dr. C. P. Oliver, who practised for many years in Maidstone, died in the West Kent General Hospital on June 3 after a short illness. He was 63 years of age.**

Charles Pye Oliver came from a distinguished family of doctors. Both his father and grandfather were practitioners in the same town before him. He was educated at Epsom College, Caius College, Cambridge, and St. Thomas's Hospital. He qualified M.R.C.S., L.R.C.P. in 1922, and took his M.B., B.Ch. in 1923. Afterwards he held the post of house-physician at St. Thomas's Hospital. He saw active service in the first world war as a subaltern in the Royal West Kent Regiment, and later joined the Territoral Army, retiring in 1937 with the rank of major. After returning from the first world war he joined his father, Colonel C. Pye Oliver, in general practice in Maidstone.

Oliver was eminently successful and held many appointments, including those of physician to the West Kent General Hospital, consultant physician to the Kent County Ophthalmic and Aural Hospital, consultant physician to Leybourne Grange Hospital, medical referee to the Kent County Crematorium Society, and certifying factory surgeon. In addition, he was a member of the management committee of the Mid-Kent Hospital Group, and a former chairman of the Maidstone Division of the B.M.A. As a young man he was interested in sport, playing rugger for the Maidstone club. He later became a keen fisherman.

L. P. McB. writes: "Pye," as he was known to his large circle of friends, had a most likable character, always down to earth and straight in everything he did and said. He abhorred everything that smacked of insincerity or pomposity. In addition, he had a great sense of humour and enjoyed life to the full. A memorial service for him, held at the West Kent General Hospital, was crowded to overflowing, and gave ample proof of the affection of the staff and the high regard in which he was held. He will be sadly missed by his partners and innumerable friends, many of whom had the privilege of being his patients. Our deep sympathy is extended to his widow and son.

## R. NAPIER, M.B., Ch.B., F.R.F.P.S.

**Dr. Robert Napier, of Dunkeld, died suddenly in Perth Royal Infirmary on June 8. He was 54 years of age.**

Robert Napier, a son of the Manse, was born at Stitchil, near Kelso, in 1907. From Hamilton Academy he went to Glasgow University, where he graduated M.B., Ch.B. in 1930. In 1936 he became F.R.F.P.S. After holding the post of house-surgeon in Glasgow Royal Infirmary he was appointed surgeon to the Church of Scotland Hospital, Aden. He came home just before the second world war to join the R.A.F. and rose to the rank of wing-commander. He intended to continue as a surgeon in civilian life, but a series of unfortunate incidents thwarted him. He had the unique experience of being involved in three railway accidents, of which one at least was very serious for him and upset his plans. Coming to Dunkeld in October, 1946, he soon became a loved and much respected physician and friend to many in this lovely part of Perthshire. He had one standard of care and treatment for his patients, rich or poor—the best that he could give. His life was one of real Christian service and he did not spare himself. Many of his patients saw him doing his rounds on the day he died, so his death came as a great shock to all in the district.

Napier was by nature a shy man, but in a small gathering of friends he was delightful company. Here his great sense of humour came out and he had a wonderful fund of anecdotes, many of them told against himself. The large attendance of consultants, fellow practitioners, patients, and friends at the Dundee Crematorium was an indication of the affection and respect in which he was held, and the feeling was left to many of us that a good friend had passed on. Much sympathy is felt for his widow and two sons, one of whom is following his father's profession.—N. M.

## J. N. MORRISON, M.R.C.S., L.R.C.P.

**Dr. J. Neill Morrison, who practised in Sheppey for many years, died in All Saints Hospital, Chatham, on June 14 at the age of 48.**

The son of the late Dr. John Morrison, John Neill Morrison was born in London in the Mile End Road. He was educated at Epsom College and the London Hospital, and qualified in 1938. During the war he held a temporary

commission in the Royal Naval Volunteer Reserve and attained the rank of Surgeon Lieutenant-Commander. He saw service in the Atlantic convoys, the landings at Narvik, the Pacific campaign, and the D-day and North African landings. During his time in Sheppey he was president or chairman of a number of local organizations, and he was divisional surgeon to the St. John Ambulance Brigade. He was a member of the Kent and Canterbury Local Medical Committee. Morrison was extremely popular with his colleagues, and in his devotion to his patients he continued to work hard even when he was quite ill. He had a delightful sense of humour, and his dry, gentle wit was nowhere more in evidence than at the medical meetings which were held in Sheppey from time to time. He will be greatly missed, and his colleagues in Sheppey send sincere sympathy to his widow and family.—M. D. L.

### A. WOODMAN, M.B., B.S.

Dr. A. Woodman, for many years in general practice in Darlington, died on June 15. He was 70 years of age.

Athelstan Woodman was a Northumbrian who went to Dollar Academy and then took his arts degree at St. Andrews University. After teaching for a short time, he entered King's College, Newcastle, and qualified in medicine. He served with the Royal Navy in the first world war, and after a short time in Alnwick as an assistant in general practice he came to Darlington in 1920 and took over Dr. Lawrence's practice. Woodman had a long and busy life, in which his outstanding abilities as a diagnostician and his intelligent treatment and understanding of his patients' problems and difficulties were very plain to all. He was a past chairman of the Darlington Division of the B.M.A. and its honorary treasurer for many years. He took a very active part in all its many activities and his advice will be greatly missed. He had served on the local executive council since the Health Service began. An accomplished sportsman in his younger days, he was a keen golfer and a very difficult opponent to beat. In his later years he took up gardening, and a great success he made of it, aided and abetted by his wife.

Woodman retired from active practice in 1958, and did not enjoy good health during his remaining years. There will be a great sense of loss, both in the community at large and especially in the medical profession. He was a good friend, a shrewd physician, and, above all, the soul of honesty. Although he had a somewhat acid manner he became the kindliest and most friendly person on better acquaintance. He is survived by his wife and five children.

### R. C. DAVENPORT, M.B., B.S., F.R.C.S.

The obituary of Mr. R. C. Davenport was published in the *Journal* of June 24 (p. 1833).

T. K. L. writes: With the passing of Robert Davenport, one more link has been lost with an age when a sense of duty and personal service was the rule rather than the exception. As dean of the Moorfields Medical School, and subsequently as dean of the Institute of Ophthalmology, Davenport laboured for 21 years organizing the courses of instruction for a vast number of postgraduate students who came to London from all parts of the British Commonwealth in order to learn ophthalmology. His was largely a personal task which involved spending many hours each week interviewing students and discussing with them their plans and their problems, rejoicing with those whose efforts in examination had met with success and consoling those who had failed.

Davenport set a fine example as a clinical teacher in the out-patient department, being always punctual in his hospital attendances and giving individual attention to each student. He was a popular lecturer and never failed to make his subject interesting and thoroughly up to date. He was kindness itself and conscientious to a degree, and, although at times acutely aware of the shortcomings of others, he was never known to make an unkind remark.

"His heart was one of those which most enamour us,
Wax to receive and marble to retain."
(Lord Byron.)

Mr. R. U. HINGORANI writes: I was deeply grieved to read about Mr. R. Davenport's death. I had known him since 1930 and must have sent hundreds of medical and other friends to see him from all the Commonwealth countries. I was very proud of knowing him. Everyone praised him for different qualities, and they remained his permanent friends abroad. It is impossible to describe all that my friends said about him in a few words. He was a perfect Englishman and true representative of Great Britain. May I through you express our deep sorrow on their behalf and on my own?

## Medical Notes in Parliament

### WORLD POPULATION AND FOOD SUPPLIES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Lord BRABAZON OF TARA introduced a motion in the House of Lords on June 28 inviting the House to declare that further development and education in the regulation of birth would contribute to world peace. The debate was woven of many strands, from his own controversial comment that "any father of three or four children has had enough," through the Anglican and Roman Catholic beliefs in what are legitimate methods of family limitation, to the unrealism of expecting women in Indian villages to use the Pincus pill. But the core of the argument was the rate of growth of world population, particularly in the Asian countries, and of world food supplies. The starting-point was the Malthusian theory of eventual starvation through over-population.

Lord Brabazon recalled that Lord Boyd-Orr had said in 1950 that a lifetime of malnutrition was the lot of at least two-thirds of mankind, and the remark had never been withdrawn. Mr. Colin Clark, of Oxford, had estimated that on the basis of Holland's standard of agriculture, proper farming could produce 1,070 tons of grain-equivalent per square kilometre of farmed land, which would support the growing population for another two centuries.

#### Advance of Medical Science

One of the contributory factors was the advance of medical science, of which Lord Brabazon gave two examples. In British Guiana insects used to cause the death of 250 in 1,000 children at birth; in three years, with the advent of D.D.T., this was reduced to 67. In Mauritius, where the population had been static, after the conquest of malaria the birth rate increased 50 per 1,000 and the death rate diminished to 10. Having set the problem, what means were to be used to solve it? Not many men and women wanted large families, but they insisted on having their elemental pleasures and would not be deprived of them on the basis of over-populating the world. It was the male who took the initiative, and it was on him that restraint should be imposed. Apart from castration, which was of course a major operation, there was vasectomy—a very slight affair which did not influence the desire or capacity for sexual union.

Lord AMULREE did not accept that because a country did not officially encourage or practise birth control it was necessarily a threat to world peace; and he instanced the need for a strong, well-populated Israel and Poland. Brazil had enormous potentialities, and the population should be encouraged to expand. If the under-developed countries got proper food and better education there would be no need to worry about the possibility of dangerous increases of population.

Lady SUMMERSKILL believed that the social and economic forces which had operated in the West would be equally effective in the rest of the world, for social progress was a by-product of economic advance. Commenting on the Family Planning Association's booklet on the rhythm method, she asked, "Can it be argued that this is a humane method, since it advises abstinence at the very time when a woman is least disposed to be abstinent? The rhythm method of birth control, besides being far from certain, thwarts women in their natural desires." The tenuous theological distinction between one method of birth control and another needed careful examination.

### Overcrowded Asian Countries

The BISHOP OF ST. ALBANS was one of the many speakers in the debate who referred to experience in India, and he told of a Madras doctor who had said, "Shocking as it may seem, in many rural areas the cost of having a baby would be cheaper than the price of birth-control equipment." But his main purpose was to reiterate the doctrine embodied in the resolution of the 1958 Lambeth Conference of responsible parenthood, of "planning in such ways as are mutually acceptable to husband and wife in Christian conscience. Theologians from many Churches were continuing their researches. They would oppose as a violation of human rights any attempt by the State to enforce family limitation, whether by compulsory sterilization, abortion, or punitive taxation on large families. They would oppose as both immoral and politically imprudent any attempt to attach compulsory family limitation as a condition of economic aid to under-developed countries.

Lord CASEY maintained that the peoples of the West were not politically aware to any appreciable extent of the vast problem of the overcrowded countries of Asia and the menace it presented to mankind. He quoted Mr. Karmarkar, the Indian Minister for Health in charge of the family planning plans, as saying, "All our efforts to achieve a higher living standard will be frustrated if we do not take effective steps to keep our population within proper limits. An important aspect of the work is the evolution of suitable and readily acceptable contraceptives." Existing methods, Lord Casey said, were unsuitable for widespread use in India. Dr. A. S. Parkes had described them as inadequate and crude. The recently evolved "enavid" pill needed to be taken 20 days in every month. To an illiterate woman in an Asian village that was far too exacting a procedure. Other methods available were either not effective or could be eliminated on the score either of inconvenience or expense. What was wanted was an oral contraceptive pill that could be taken once or twice a month; and this was not even beginning to be in sight. Appreciable research was going on, but not nearly enough. He was firmly of the belief that food production could not possibly keep pace with population increase; and that the evidence was incontrovertible that family planning was the only possible solution, *vide* the fact that in India and Pakistan it had been adopted as official Government policy.

### Production of Animal Protein

Viscount HAILSHAM, Lord President of the Council and Minister of Science, from the mass of estimates of uncertain value accepted that world population was increasing fast, and also that food production was increasing somewhat faster than population, but unevenly. Assuming a world population in 1980 as something like 4,000 millions, and by the year 2000 as 6,000 millions, world cereal production must be increased by one-third before 1980 and doubled by 2000. The production of animal proteins, in many ways more important, should be doubled by 1980 and quadrupled by 2000. This required drastic action, and in his opinion was not receiving the attention it deserved. Yet it was an objective at least as worthy of humanity as a space station on the moon or a trip to Mars. To double the food supply might be more easily achieved than halving the population by any means short of genocide. There was a great deal of room for increased and improved methods of agriculture, and serious methods of research into improving food supplies, which ought to be considered much more seriously. The debate had included evidence that not enough was known about the factors influencing decline of growth in populations, and the methods used. It might be well to encourage research into demography and human relations. He enunciated two political principles. The first was a genuine belief that, at least in conditions such as those in Britain, any method of birth regulation was an ultimate question of personal conduct and conscience; it should not be made a matter of social or political pressure in either direction. Existing practice made information readily available, but in confidence. The second was that he was fundamentally opposed to international interference. It was an extremely sensitive international topic. Social policy was surely part of sovereignty. This country should not interfere. If it was asked for its view it could be given in confidence.

The motion, having served its purpose, was withdrawn.

## PRESCRIPTION CHARGES

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The least severe of the criticisms levelled against the Minister of Health by Mr. L. PAVITT (Willesden, West, Lab.) in connexion with the increased prescription charge—a topic which, after many questions, he brought on to the floor of the House for a short debate on June 23—was, "I am astounded that so intelligent a person could be so mistaken in policy." And his final objurgation was, "I ask the Minister to reverse his policy, or make room for someone who will."

### Protests by Executive Councils

There was overwhelming evidence, Mr. Pavitt claimed, that doctors, chemists, and patients were against it, and one in three of the executive councils had protested too, but all this had been contemptuously swept aside. The Minister had estimated a 2% drop in prescriptions, but between February and March this year it had been 22%—from 22.2 million items to 17.5 million. Compared with March, 1960, there had been a drop of 13%. The whole conclusion that the Hinchliffe Committee had drawn from the previous imposition of prescription charges had been ignored. Even worse was the Minister's flouting of the specific recommendation that, if any change in the basis of charge was contemplated, it should be preceded by an inquiry to assess the probable effects. The new charge had brought claims for increased payment by pharmacists. The doctor–patient relationship was being destroyed, especially for the 2,500 dispensing doctors, who were made to act as tax collectors, and for whom it was an appalling burden. It was socially unjust, because it hit the hard-working, poorer section of the community who were not on assistance.

### Prescriptions in May Unaltered

Miss EDITH PITT, Parliamentary Secretary to the Ministry of Health, added one new ingredient to the prescription as before—the fact that the number of prescriptions dispensed in May was 16.9 million, which she said was in the same range as the May figures in the previous four years. This was used to support her argument that there was no evidence of any significant change in prescribing habits as a result of the increased charge. The number of items dispensed in January, 1961, was 23.7 million and in February 22.2 million—both figures, she pointed out, being higher than at any corresponding time in the previous four years except for February, 1959. The provisional figures for March this year, 17.5 million, and April, 15.2 million, were probably below those for the corresponding months in the same period. She repeated the Minister's argument that March and April was too short a period to draw conclusions from, and that nothing less than the experience of a full

year could disclose any trends that could be interpreted as evidence that people were not getting the prescriptions they needed. The Minister's estimate of 2% related to a full year. He was satisfied that the revised basis of charge in 1956 had resulted in a substantial reduction in the net cost to the Exchequer; and he expected that the recent doubling of the charge would mean that the cost of the pharmaceutical services for 1961–2 would be substantially less than if the 1s. charge had remained in operation. The Government had never committed itself to accepting the Hinchliffe recommendation for a preliminary inquiry.

### Cases of Hardship

The Minister had several times offered to look into cases where it was alleged the charges were producing hardship. They had no evidence at the Ministry that standards of treatment had been affected by inability to pay the charges. She would expect that doctors and pharmacists would bring such evidence to the notice of the Minister immediately. She could see nothing wrong in the discussion between doctor and patient of the number of items or quantities on a prescription, and hence the frequency with which the patient would have to pay the prescription charge. There was no reason why information about the price of a drug or dressing should undermine confidence in a doctor.

## QUESTIONS IN THE COMMONS

### Money for Cancer Research

On June 27 Sir LEONARD ROPNER (Barkston Ash, Con.) asked the Parliamentary Secretary for Science what was the total amount spent on cancer research during the last period of 12 months for which figures were available; what proportion of the total amount was provided from public funds; and what proportion came from voluntary contributions. Mr. DENZIL FREETH told him that complete figures for expenditure on cancer research were not available, but the total amount spent by the Medical Research Council and the two major voluntary organizations, the British Empire Cancer Campaign and the Imperial Cancer Research Fund, in 1959–60 was about £1,541,400. Of this sum 37.6% was provided from public funds and 62.4% from voluntary contributions.

### Reclassification of Mental Patients

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on July 3 whether, in the light of the judge's comments in the case of Derek Sowle, he would appoint a committee of inquiry to report on this and other cases in which mental and mental defective patients had been responsible for crimes of violence. Other questions by Mr. M. LIPTON (Brixton, Lab.) mentioned that Sowle had been ordered to be detained in Rampton for 40 years; and by Mr. MARTIN MCLAREN (Bristol, North-west, Con.) that he was convicted on June 29 at Bristol Assizes of manslaughter, and had been reclassified three days before the commission of the offence of which he was convicted; and asked for inquiry to be made. Mr. ENOCH POWELL stated that investigation was being made, and he would make a further statement.

### Manchester Report on Drug Costs

Mr. ARTHUR HOLT (Bolton, West, Lib.) asked the Minister if he had received the report of the investigation into the cost of 3,000 different drugs and dressings carried out by the Manchester Regional Hospital Board; and to what extent its recommendations went beyond those of the Cohen Committee. Mr. POWELL replied that he had seen the report of certain actions to reduce the exceptionally high cost of drugs and dressings at the Royal Lancaster Infirmary. There was no inconsistency between these actions and anything in the Cohen Committee's reports on prescribing by general medical practitioners.

### London Postgraduate Hospitals

Mr. K. ROBINSON asked what changes in administrative structure would be required as a result of the decision to group a number of postgraduate hospitals and institutes. Mr. POWELL: None, apart from a change in the administration of St. Mark's Hospital.

# Vital Statistics

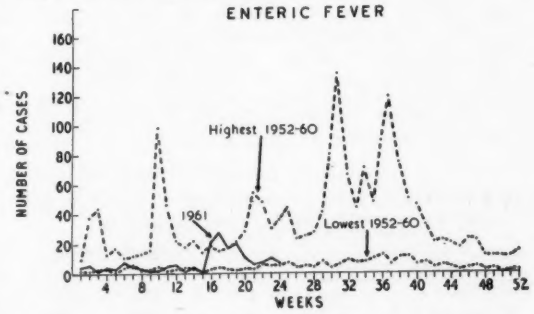
### Industrial Accidents and Diseases

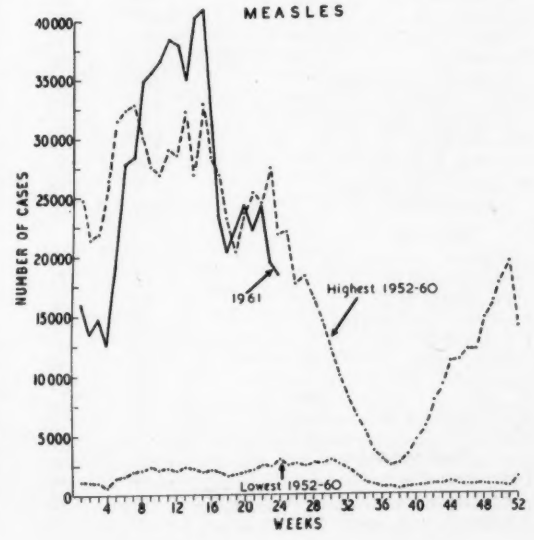
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in May was 92, compared with 81 in the previous month and 85 in May, 1960.

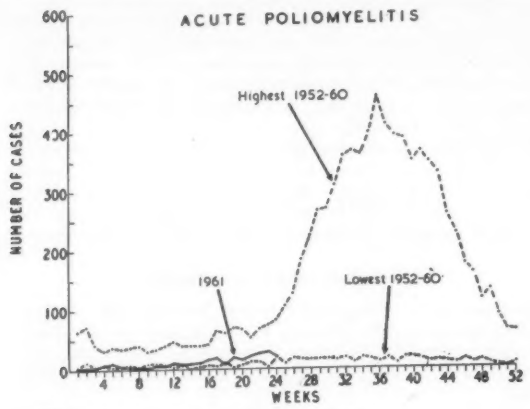
The numbers of cases of industrial diseases in the United Kingdom reported during May were as follows: lead poisoning 6, compressed air illness 4, anthrax 2, epitheliomatous ulceration 16, chrome ulceration 6: total 34. There were two deaths from epitheliomatous ulceration.

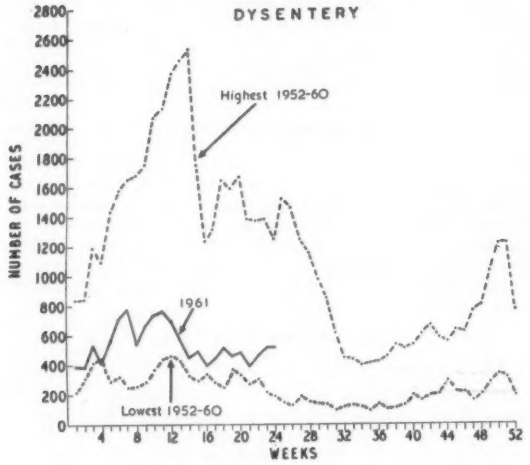
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.






### Infectious Diseases

*Areas where the numbers of notifications were high in the latest two weeks for which figures are available.*

| | Week Ending June 17 | Week Ending **June 24** |
|---|---|---|
| **Measles** | | |
| Devonshire | 618 | **535** |
| Plymouth C.B. | 310 | **220** |
| Gloucestershire | 1,005 | **690** |
| Bristol C.B. | 365 | **208** |
| Staffordshire | 1,402 | **962** |
| Stoke-on-Trent C.B. | 366 | **348** |
| Sussex | 601 | **557** |
| Brighton C.B. | 171 | **207** |
| Warwickshire | 407 | **471** |
| Birmingham C.B. | 204 | **293** |
| Yorkshire West Riding | 1,378 | **1,272** |
| Sheffield C.B. | 287 | **225** |
| **Dysentery** | | |
| Lancashire | 140 | **115** |
| Liverpool C.B. | 16 | **29** |
| Fleetwood M.B. | 34 | **26** |
| Yorkshire West Riding | 96 | **76** |
| Leeds C.B. | 31 | **24** |
| Earby U.D. | 5 | **30** |
| Glasgow | 81 | **104** |
| Dundee | 39 | **28** |
| Edinburgh | 21 | **18** |
| **Food-poisoning** | | |
| Lancashire | 16 | **90** |
| Preston R.D. | 0 | **78** |
| London | 10 | **35** |

## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **June 17** (No. 24) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES | 1961 Eng. & Wales | 1961 Lond. | 1961 Scot. | 1961 N. Ire. | 1961 Eire | 1960 Eng. & Wales | 1960 Lond. | 1960 Scot. | 1960 N. Ire. | 1960 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria | 4 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | |
| Dysentery | 517 | 34 | 164 | 2 | 11 | 965 | 130 | 129 | 8 | 9 |
| Encephalitis, acute | 1 | 0 | | 0 | | 2 | 0 | 1 | 0 | |
| Enteric fever: | | | | | | | | | | |
| Typhoid | 2 | 0 | 1 | 0 | | 0 | 0 | 0 | 0 | |
| Paratyphoid | 5 | 0 | 1 (B) | 0 | 1(B) | 8 | 1 | 0 | 0 | |
| Food-poisoning | 389 | 10 | 12 | 3 | | 468 | 34 | 14 | 4 | |
| Infective enteritis or diarrhœa under 2 years | | | | 10 | 31 | | | | 11 | 42 |
| Measles* | 18,569 | 440 | 298 | 333 | 182 | 2,936 | 122 | 53 | 3 | 4 |
| Meningococcal infection | 19 | 1 | 11 | 0 | | 17 | 0 | 9 | 0 | |
| Ophthalmia neonatorum | 7 | 0 | 3 | 0 | | 25 | 2 | 6 | 0 | |
| Pneumonia† | 199 | 12 | 107 | 1 | 2 | 211 | 9 | 126 | 2 | 2 |
| Poliomyelitis, acute: | | | | | | | | | | |
| Paralytic | 14 | 0 | 3 | 2 | | 15 | 3 | 0 | 0 | 9 |
| Non-paralytic | 6 | 0 | | | | 5 | 2 | 0 | | |
| Puerperal fever§ | 159 | 21 | 6 | 3 | | 173 | 20 | 9 | 3 | |
| Scarlet fever | 420 | 18 | 30 | 26 | 8 | 346 | 7 | 44 | 12 | 13 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | 385 | 47 | 72 | 15 | | 451 | 53 | 82 | 10 | |
| Non-respiratory | 62 | 6 | 11 | 1 | | 65 | 5 | 9 | 2 | |
| Whooping-cough | 443 | 17 | 53 | 4 | 35 | 1,486 | 112 | 235 | 11 | 22 |

| DEATHS | 1961 Eng. & Wales | 1961 Lond. | 1961 Scot. | 1961 N. Ire. | 1961 Eire | 1960 Eng. & Wales | 1960 Lond. | 1960 Scot. | 1960 N. Ire. | 1960 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysentery | 1 | 0 | | 0 | | 3 | 1 | | 0 | |
| Encephalitis, acute | | 0 | | | 0 | | 0 | | | 0 |
| Enteric fever | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | |
| Infective enteritis or diarrhoea under 2 years | 10 | 0 | 3 | 0 | 0 | 6 | 0 | 2 | 0 | 0 |
| Influenza | 8 | 0 | 1 | 0 | 1 | 11 | 0 | 0 | 0 | 0 |
| Measles | | 1 | 1 | 0 | 1 | | 0 | 0 | 0 | 0 |
| Meningococcal infection | | 1 | 0 | | | | 0 | 1 | | |
| Pneumonia | 428 | 27 | 17 | 16 | 5 | 392 | 24 | 10 | 14 | 2 |
| Poliomyelitis, acute | 0 | 0 | | 0 | 0 | 0 | 0 | | 0 | 2 |
| Scarlet fever | | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Tuberculosis: | | | | | | | | | | |
| Respiratory | 51 | 6 | 7 | 0 | 2 | 58 | 5 | 3 | 1 | 3 |
| Non-respiratory | | 1 | | 0 | 1 | | 0 | 1 | 0 | 0 |
| Whooping-cough | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Deaths 0–1 year | 311 | 33 | 23 | 5 | 10 | 296 | 18 | 29 | 7 | 10 |
| Deaths (excluding stillbirths) | 9,092 | 681 | 537 | 121 | 139 | 8,740 | 627 | 513 | 142 | 126 |
| **LIVE BIRTHS** | 16,175 | 1372 | 1061 | 309 | 460 | 16,377 | 1334 | 1008 | 289 | 420 |
| **STILLBIRTHS** | 308 | 21 | 16 | | | 310 | 19 | 29 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

**Fullerian Professor of Physiology, Royal Institution**

Professor R. J. HARRISON, University of London professor of anatomy at the London Hospital Medical College since 1954, has been elected Fullerian professor of physiology, Royal Institution, in succession to Professor J. Z. YOUNG, F.R.S. The professorship was endowed in 1834 by John Fuller, an early benefactor of the Royal Institution, and is normally held for three years.

Professor Harrison, who is 40, was educated at Oundle, and Gonville and Caius College, Cambridge, and received his medical training at St. Bartholomew's Hospital Medical College. He has held appointments at Glasgow University and Charing Cross Hospital, and is joint author of *Anatomical Terms* and author of *Man the Peculiar Animal* in addition to numerous papers on embryology and comparative and human anatomy. He is especially known for his research on the physiology of diving seals.

**College of G.P.s' Card Index Publications**

The College of General Practitioners issues a series of record cards, all of which are designed to fit into the N.H.S. envelope, and which may be obtained both by members and by non-members of the College. The series includes an obstetric record card and a summary card (both costing 12s. 6d. per 100), and a menstruation chart (16s. per 100). There are also sets of cards printed in French, Spanish, Italian, German, Hungarian, and Polish which are designed to assist in taking a history when the patient has little or no English. The sets cost 5s. These publications may be obtained from the Secretary of the College, 41 Cadogan Gardens, London N.W.3.

**Domiciliary Midwifery Symposium**

The Royal College of Obstetricians and Gynaecologists, in conjunction with the College of General Practitioners, has arranged a symposium on "Domiciliary Midwifery," primarily—though not exclusively—for general practitioners who are Diplomates of the R.C.O.G. It will be held in the Royal College on October 18.

The morning session will be devoted to "The Avoidable Factor in Maternal Mortality." The selection of cases for domiciliary confinement, toxaemias of pregnancy, haemorrhage, and the place of the Flying Squad will be considered briefly by Sir JOHN PEEL, Professor T. N. A. JEFFCOATE, Mr. ARNOLD WALKER, and Mr. FRANK STABLER. The afternoon session will be devoted to the staffing and management of a general-practitioner-obstetrician unit and the part it should play in the Obstetric Services. The opening speakers include two consultants, Mr. JOHN STALLWORTHY and Mr. R. A. TENNENT, and two general practitioners, Dr. T. MAURICE and Dr. P. B. BAILEY. Those wishing to attend should apply before October 4 to the Secretary, Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London N.W.1.

**British Paediatric Association**

The British Paediatric Association held a joint annual meeting with the Canadian Paediatric Society at Cambridge from June 27 to 29. The meeting was attended by over 300 doctors, of whom 50 were Canadians. During the meeting Dr. J. H. EBBS, of Toronto, delivered the George Frederic Still Memorial Lecture. At the B.P.A.'s annual dinner, held in the Guildhall on June 29, the first awards of the James Spence Medal were made to Professor A. A. MONCRIEFF, of London, and Professor R. A. MCCANCE, F.R.S., of Cambridge. The gold medals commemorate the late Sir James Spence and are awarded for outstanding contributions to the advancement or clarification of paediatric knowledge. The following have been elected as officers of the B.P.A. for the year 1961–2: *president*, Professor A. A. MONCRIEFF; *president-elect*, Dr. C. F. HARRIS; *treasurer*, Professor A. G. WATKINS; *secretary*, Dr. E. W. HART.

**Royal College of Surgeons' Honorary Fellows**

The Honorary Fellowship of the Royal College of Surgeons of England has been conferred on Sir HOWARD FLOREY, P.R.S., professor of pathology in the University of Oxford, and Dr. OWEN H. WANGENSTEEN, chairman, department of surgery, University of Minnesota, and former President of the American College of Surgeons.

**Society for Relief of Widows and Orphans of Medical Men**

On the last day of last year the Society had 140 members, two new members being elected during the year. There were 23 widows in receipt of grants—one fewer than the previous year. During the year one widow died at the age of 98, having been receiving grants since 1914. The Brickwell Fund distributed £530 in extra grants to widows and orphans, and special training grants to orphans over 16. The total amount distributed by the ordinary and Brickwell Funds combined was £4,205. There was a favourable balance at the end of the year of £1,406, and the mean market value of the Society's investments was £107,989 14s. 6d. The Society's address is 11 Chandos Street, Cavendish Square, London W.1.

**Council for Professions Supplementary to Medicine**

The Professions Supplementary to Medicine Act, 1960, came into force on July 1. The members of the Council for Professions Supplementary to Medicine, which now comes into existence, include Professor ROLAND BARNES, Professor J. MCCLURE BROWNE, Dr. H. A. BURT, Dr. J. D. CAMERON, Dr. G. A. CLARKE, and Dr. J. O. F. DAVIES. The Supplementary Professions represented on the Council are chiropody, dietetics, medical laboratory technology, occupational therapy, physiotherapy, radiography, and remedial gymnastics. The first tasks of the Council will be to appoint a Registrar and his staff and to set up the Registration Boards for each of the seven professions.

**Hospital Building Notes**

The latest in the Ministry of Health's series of Hospital Building Notes, No. 19, *Department of Medical Photography and Medical Illustration*, gives guidance on the design of a medical photography and medical illustration department for general hospitals, including teaching hospitals. (H.M.S.O., 1s. 6d. net.)

**Cutting Drugs Bill**

It was reported at a meeting of Manchester Regional Hospital Board's finance committee that an economy drive in eight hospitals in the Lancaster and Kendal area had reduced the annual bill for drugs and dressings by between 10 and 20%. After an investigation had shown the wide price range of drugs, which fulfilled the same or similar functions equally satisfactorily, prescriptions were standardized, by agreement, and where no advantage was to be gained by using an expensive drug a cheaper one was preferred.

**Illegal Traffic in U.S. Drug Samples**

According to the United States Food and Drug Administration there is a widespread traffic in the U.S. in the free drugs sent to doctors by pharmaceutical firms. The samples are bought at about 10% of the wholesale price, are relabelled by untrained personnel, sold to chemists' shops for 80% of the wholesale price, and then resold to customers at the usual retail price. In June the Administration seized $170,000 worth of jumbled-up drug samples—including antibiotics, hormones, and tranquillizers—from bootleggers in the New York and Chicago areas. "Some day," says Dr. K. MILSTEAD, the director of the F.D.A.'s regulatory division, "someone is going to get the wrong drug in the wrong bottle." (*Newsweek*, June 26.)

**Faculty of Radiologists**

The following officers have been elected for 1961–2: *president*, Dr. ROHAN WILLIAMS (London); *vice-presidents, radiodiagnosis*, Dr. ERIC SAMUEL (Edinburgh), and *radiotherapy*, Dr. R. C. TUDWAY (Bristol); *warden of the fellowship*, Professor R. MCWHIRTER (Edinburgh); *honorary treasurer*, Dr. E. C. EASSON (Manchester); *honorary secretary*, Dr. C. J. HODSON (London); *honorary editor*, Dr. D. SUTTON (London).

**Association of Anaesthetists of Great Britain and Ireland**

The Association of Anaesthetists of Great Britain and Ireland has awarded Research Essay Prizes in 1961 to Dr. J. D. ROBERTSON and Dr. A. WYNN WILLIAMS (Royal Infirmary, Edinburgh), Dr. A. C. FORRESTER and Mr. J. Brown (Royal Infirmary, Glasgow), and Mr. D. G. CALVERT (Westminster Children's Hospital, London). Regulations for the 1962 Research Essay Prizes can be obtained from the Honorary Secretary of the A.A.G.B. and I. at 47 Lincoln's Inn Fields, London W.C.2.

**Institute of Child Health**

The United Nations Children's Fund has approved a grant of about £17,800 to the Institute of Child Health, University of London. Detailed plans have not yet been completed, but the Institute hopes to provide one-year training courses in teaching, administration, and the organization of research for six potential heads of paediatric departments from countries in the Middle and Far East where English is spoken in medical schools.

**In Brief**

The Lord Kitchener National Memorial Fund has offered, since 1952, a yearly prize of 100 guineas for the best student of the year at the Kitchener Memorial Medical School at Khartum. In place of the prize it is hoped next year to award a more valuable postgraduate scholarship which will enable a student to pursue his studies in London.

**People in the News**

▶ Mr. H. S. TAYLOR-YOUNG has succeeded Major A. C. WHITE KNOX as surgeon-in-chief of the St. John Ambulance Brigade.

▶ In recognition of his services as librarian to the Liverpool Medical Institute Mr. W. A. LEE is to receive the honorary degree of M.A. of Liverpool University.

▶ At the National Rose Society's annual show in London Dr. T. M. CULLINGWORTH, of Shrewsbury, was awarded the Franklin Dennison Bowl for a vase of hybrid tea roses, and Dr. S. W. DRINKWATER, of Norwich, gained the amateurs' prize for the best bloom in the show with a specimen of "Premier Bal."

## COMING EVENTS

**Biochemical Society.**—Meeting, July 13–14, department of biochemistry, Oxford University. July 13, 10.40 a.m., original communications; 2 p.m., "The Training of Biochemists." July 14, 10.15 a.m., original communications.

**Royal College of Surgeons of Edinburgh.**—Professor R. MILNES WALKER, "Some Aspects of Liver Disease," July 14, 3.30 p.m., in the Hall of the College. Open to postgraduate students.

**Royal Commonwealth Society for the Blind.**—Annual general meeting, July 18, 3 p.m., Assembly Hall, Church House, Great Smith Street, London S.W.1.

**Cambridge University School of Clinical Research and Postgraduate Medical Teaching.**—Sir ERNEST MARSDEN, F.R.S. (member of New Zealand Atomic Energy Committee), "Radioactivity of Soils, Food-Plants and Bones, with Special Reference to Niue Island," July 19, 4.15 p.m., Postgraduate Lecture Room, Addenbrooke's Hospital, Cambridge.

**"Chest Diseases in Children."**—Symposium, including panel discussion on "Pulmonary Tuberculosis in Children," July 26, 11.20 a.m., Whittington Hospital, Museum Lecture Theatre, Archway Wing, Archway Road, London N.19. Details from Dr. P. D. B. DAVIES, St. Pancras Chest Clinic, 26 Margaret Street, London W.1.

**Cambridge University School of Clinical Research and Postgraduate Medical Teaching.**—Professor G. H. GLASER (associate professor of neurology and head of the section of neurology, Yale University School of Medicine), "Bioelectric Properties of Dystrophic Muscle," July 26, 4.15 p.m., Postgraduate Lecture Room, Addenbrooke's Hospital, Cambridge.

**University of London Postgraduate Medical School.**—Advanced symposium for consultants, "Modern Aspects of Cardiovascular Radiology," September 21–23. (See advertisement p. 53.)

**London School of Hygiene and Tropical Medicine.**—Whole-time course in occupational health for medical practitioners, September 25–December 15. See advertisement p. 53. Whole-time courses in occupational hygiene for graduates (in special circumstances, non-graduates), the first beginning on October 2. See advertisement p. 53.

## NEW ISSUES OF SPECIALIST JOURNALS

*The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.*

### ANNALS OF THE RHEUMATIC DISEASES

**Obituary. Jan van Breemen.**
**Sulphate ($^{35}SO_4$) Fixation by Human Articular Cartilage Compared in the Knee and Shoulder Joints.** D. H. Collins and G. Meachim.
**Psoriatic Arthritis.** V. Wright.
**The Nature of Anaemia in Rheumatoid Arthritis. V. Red Cell Survival Measured by Radioactive Chromium.** J. Richmond, W. R. M. Alexander, J. L. Potter, and J. J. R. Duthie.
**Sarcoidosis Presenting with Polyarthritis.** Michael J. Williams.
**Effects of Environmental Temperature upon Capillary Resistance in Patients with Rheumatoid Arthritis and Other Individuals.** J. L. Potter and J. J. R. Duthie.
**Rheumatic Complaints in a Rural Population.** Joan M. Bremner.
**A Controlled Trial of Phenylbutazone, Oxyphenbutazone, and a Placebo in the Treatment of Rheumatoid Arthritis.** R. I. Meanock and E. Lewis-Faning.
**Combined Aspirin and Cortisone Treatment of Acute Rheumatic Fever.** J. D. H. Slater.
**Placebo Responses in an Arthritis Trial.** R. A. H. Morison, A. Woodmansey, and A. J. Young.
**Puerperal Hyperuricaemia.** B. L. J. Treadwell and A. St. J. Dixon.
**Atrophic Polychondritis.** H. Rhys Davies and A. R. Kelsall.
**Book Review.**
**Heberden Society.**
**Abstracts.**

Volume 20, No. 2. (Quarterly; £3 annually.)

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

**Tuesday, July 11**

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., F. E. Williams Lecture by the Reverend A. T. Welford, M.A.: On Changes of Performance With Age.

SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., discussion, to be introduced by Dr. M. M. Glatt: The Role of the Recovered Alcoholic in furthering Education regarding Alcoholism.

**Wednesday, July 12**

POSTGRADUATE MEDICAL SCHOOL OF LONDON: EXPERIMENTAL RADIOPATHOLOGY RESEARCH UNIT.—At Wolfson Institute, Hammersmith Hospital, 2 p.m., Dr. Konrad Bloch (Harvard University): Studies on Lipid Biosynthesis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor G. W. Milton: Behaviour of Gastric Epithelium under Various Conditions.

**Thursday, July 13**

GROUP FOR REPRESENTATION OF THE VIEWS OF CLINICAL PSYCHIATRISTS.—At Rygate Room, Tavistock House North (Fourth Floor), Tavistock Square, W.C., 5.30 p.m., committee meeting.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At West London Hospital (Lecture Room), 5.30 p.m., annual general meeting. Election of officers, etc.

## BIRTHS, MARRIAGES, AND DEATHS

### DEATHS

**Cox.**—On June 8, 1961, at the home of his daughter, Ford Farm, Coleford, near Crediton, Devon, Alfred Berridge Cox, M.B., Ch.B., Surgeon Captain, R.N., retired, of 11 Glenwood Road, Mannamead, Plymouth, Devon, aged 81.

**Gayer.**—On June 13, 1961, Lena Bella Gayer, M.R.C.S., L.R.C.P., of 14 Edith Road, West Kensington, London W.

**Klepacz.**—On May 22, 1951, Marcel Klepacz, M.D.(Warsaw).

**Napier.**—On June 8, 1961, at Perth Royal Infirmary, Robert Napier, M.B., Ch.B., F.R.F.P.S., of Tay Terrace, Dunkeld, Perthshire.

**Pinker.**—On June 1, 1961, at Weir House, Countess Wear, Exeter, Henry George Pinker, F.R.C.S.

**Young.**—On June 3, 1961, at his home, Foxley Henning, Raughton Head, Carlisle, Cumberland, James Wilson Young, M.B., Ch.B.

# Any Questions ?

*We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.*

### Creaking Knees

**Q.**—*A healthy man in his middle thirties has suffered from creaking knee-joints for the past two or three years. It is worse in the right knee, and he is really only aware of the symptom on climbing stairs. There are no other signs in the knees or any other joints, nor is there a rheumatic history. Is any treatment other than reassurance advisable, and is such a joint more likely to develop osteoarthritis in later life?*

**A.**—The fact that a joint makes a noise does not necessarily mean that an arthritic condition is present. The reason for some joints becoming noisy is not precisely known, but it is thought that the creaking may be produced by changes in air pressure within the joint. These are rather like the snapping joints which children can sometimes produce in their fingers by pulling them out quickly.

If there are no clinical signs of arthritis in the knee-joints, such as warmth, swelling, tenderness, or limitation of movement, the patient can be reassured that his creaking knees are no more likely to develop arthritis than silent ones.

### Treatment of Stings

**Q.**—*What is the best treatment which can be carried out by a person who has been stung by a bee or a wasp?*

**A.**—When a bee stings she leaves her sting and poison sac in the victim, so, if seen, it should be promptly scraped out with a finger nail, or, if not seen, wiped out with a handkerchief. It should not be picked out, for this would squeeze more poison out of the poison sac. Wasps do not leave their sting behind. Blue bag and bicarbonate of soda are often recommended as first-aid treatment; while better than nothing, they are not as good as an antihistamine cream. This, if rubbed in promptly, may mitigate the reaction.

When a sting causes shock or a severe local reaction (or if a wasp is swallowed in a drink), a doctor's advice should be sought. Often a bee-keeper has an emergency box for prompt use. Adrenaline injection, B.P. (1 in 1,000), 0.5 ml. should be injected subcutaneously, followed by cortisone acetate 50 mg. intramuscularly and an antihistamine tablet by mouth. Adrenaline is available in special injectors for immediate use, and could be given by this means by a layman in an emergency if he had been instructed in their use.

### Duties of a Domiciliary Nurse

**Q.**—*Must an instruction on treatment from a doctor to a domiciliary nurse be in writing, or does this apply only to certain treatments? If so, which? Is it a domiciliary nurse's duty to lay out a corpse?*

**A.**—This depends entirely on the doctor–nurse relationship. In an ordinary case it is perfectly proper for the doctor to give the district nurse instructions over the telephone, provided he speaks to the nurse herself and does not leave a verbal message with someone at her home. He should not leave verbal instructions with the patient or relatives to be passed on to the nurse.

When drugs scheduled under the Dangerous Drugs Regulations are to be given or any unusual treatment is prescribed, it is, of course, necessary for instructions to be given in writing. The home nurse leaves a message slip in an envelope on which messages and directions should be written in ink by the doctor.

It is not a domiciliary nurse's duty to lay out a corpse. A nurse who is in attendance on a patient who dies while she is there usually performs the last offices out of decency and thought for the relatives. The nurse will undertake the last offices when the body is in such a condition that it is likely to cause undue distress to the relatives or difficulty to the undertaker. Strictly speaking, it is the undertaker's responsibility to lay out a body. The above particulars relate to home nurses only. The rules of the Central Midwives Board make it quite clear that "a midwife must not lay out a dead body for burial except in the case of a patient on whom she had been in attendance at the time of death in the capacity of midwife or nurse."

### Prostatism

**Q.**—*What is meant by "prostatism," and is surgical intervention indicated?*

**A.**—Reference to three different textbooks which happened to be immediately available reveals that Russel Howard[1] regarded "prostatism" as a nervous disturbance of the prostate and grouped it under the "neuroses." De Illyés[2] refers to Guyon's phrase of *prostatisme sans prostate* —meaning the symptoms of a prostatic lesion without enlargement of the gland—while Austin Dodson[3] uses the word prostatism to include all obstructive lesions of the bladder neck and posterior urethra. It is little wonder that the word is not used by British urologists to-day except in inverted commas, and then only to indicate vague prostatic symptoms for which there is no obvious cause and—of more importance—for which there is no sure treatment.

However, it must be admitted that on occasion one encounters a man in the fourth or fifth decade who has no enlargement of the prostate and no evidence of bladder-neck obstruction or of urinary infection but who has increased frequency and urgency of micturition, occasional difficulty in starting, perhaps exaggerated by the presence of other persons, and vague symptoms referable to the genitalia, together with loss of libido, etc. A more fashionable term for this syndrome to-day is "chronic non-specific prostatitis," but since this implies an infective condition, proof of which is seldom forthcoming, this is again an unsatisfactory label.

The fact that prostatic massage, urethral sounds, short-wave diathermy, transurethral resection of the prostate, and, of course, all the known antibiotics have been variously recommended indicates the unsatisfactory response to treatment.

One thing is certain: prostatectomy should be performed only if the prostate is enlarged or if it is causing obstruction. Operation merely for the relief of symptoms (in the absence of obstruction) is nearly always disappointing.

REFERENCES

[1] Howard, R., in *A System of Surgery*, by C. C. Choyce, 1932, vol. 2, Cassell London.
[2] de Illyés, G., *Surgical Urology*, 1943, vol. 2. Constable, London.
[3] Dodson, A. I., and Hill, J. E., *Synopsis of Genitourinary Diseases*, 1956, 6th edition. Henry Kimpton, London.

### Purpura Associated with Thalidomide

**Q.**—*A patient of mine is suffering from a generalized purpura and haemorrhagic rash which developed two or three days after taking "distaval" (thalidomide). Does distaval belong to the carbromal group of drugs? What treatment is recommended for such a patient apart from stopping the distaval?*

**A.**—Thalidomide is a synthetic derivative of glutamic acid and it is not chemically related to carbromal, which is bromodiethylacetyl urea. Until recently it was thought that thalidomide was a useful mild hypnotic which was well tolerated and free from serious toxic effects. Within the last few months, however, a number of reports[1 2 3] have appeared suggesting that thalidomide can give rise to side-effects. The symptoms reported so far have been mainly neurological and they have appeared in patients who have been taking the drug for several months. So far as I am aware there have been no reported cases of blood dyscrasias

attributed to thalidomide, but in view of its chemical composition it would not be surprising if these did occur. In the present case the questioner does not mention whether the purpuric rash was associated with any reduction in the platelet count, so that it is uncertain whether the purpura is of the thrombocytopenic variety, like that due to apronal, or whether it is allergic in nature. In any case the majority of cases of drug-induced purpura respond rapidly to the withdrawal of the causative substance. Only if it is essential to continue the drug or if the purpura persists in spite of withdrawal should other measures, such as the administration of adrenal corticosteroids, be considered.

REFERENCES

1 Florence, A. L., *Brit. med. J.*, 1960, **2**, 1954.
2 Burley, D. M., ibid., 1961, **1**, 130.
3 Kuenssberg, E. V., Simpson, J. A., and Stanton, J. B., ibid., 1961, **1**, 291.

### Surgery for Chronic Glaucoma

**Q.**—*Is there conclusive proof that patients with chronic primary glaucoma, uncontrolled by medical treatment, are better off with surgery?*

**A.**—There is no conclusive proof that surgery prevents further loss of visual function in chronic simple glaucoma, and some reviews of results of treatment[1] have suggested that medical treatment is more effective than surgical. It must be remembered, however, that surgical treatment is usually undertaken only in cases that are progressing unfavourably on medical therapy. There is evidence[2,3] that control of ocular tension is of great importance in preventing further loss of visual field, and in cases uncontrolled by medical therapy the risks involved in surgery must be accepted as a better alternative than the inevitable progression of the disease on ineffective medical treatment.

REFERENCES

1 Walker, W. M., *Trans. ophthal. Soc. U.K.*, 1960, **80**, 473.
2 Perkins, E. S., *Acta XVIII Concilium Ophthalmologicum, Brussels, 1958*, 1959, **1**, 909. Imprimerie Médicale et Scientifique, Brussels.
3 Weekers, R., ibid., 1959, **1**, 873.

### Quarantine for Infective Hepatitis

**Q.**—*Should there be a quarantine period for patients with infective hepatitis and for their contacts, and, if so, for how long?*

**A.**—Patients with symptoms of infective hepatitis require treatment. Quarantine is a matter for consideration for those in contact. The general principle of quarantine as a means of control of infectious disease is to restrict the movements and freedom of action of susceptible contacts likely to have been exposed for the full incubation period of the disease. In practice this has been proved to be most effective in those diseases in which the incubation period is not unduly prolonged, fairly uniform, and in which clinical disease can be expected at the end of that period—for example, measles, smallpox, chickenpox, and so on. This also holds good for rabies, for, despite the long incubation period (on an average 1–3 months), symptoms of rabies can be expected in animals incubating the disease. These conditions do not pertain in infective hepatitis. The incubation period is long, varying from 14 to 42 days (average about 28 days), and the clinical pattern extremely variable. This is well shown by outbreaks of hepatitis in families and institutions. All grades of infection are encountered from asymptomatic, seen most commonly in children, to severe hepatitis with profound jaundice. But the first case of jaundice is not necessarily the first case of hepatitis. Under these circumstances quarantine measures are hardly practicable. Unfortunately, it is not possible to distinguish between immune and susceptible in the absence of a clear-cut history of hepatitis with jaundice, as the virus has not yet been isolated in the laboratory, and, therefore, no specific diagnostic tests are available. But, although quarantine measures are not recommended, the natural history of the disease provides an opportunity to suppress the infection in those exposed by prophylactic use of gamma globulin. Doses of approximately 0.06–0.12 ml. per lb. (0.45 kg.) of body weight have been shown to protect, and it may be that even smaller doses are effective.[1] Passive protection can be expected to last for 6–8 weeks, possibly for longer. Some restriction should be placed on those who have had hepatitis. They should not be allowed to act as blood donors and they should not be allowed to handle food until it is reasonably certain that they are no longer infectious. Stools should be regarded as potentially infectious for one month after the onset of symptoms.

REFERENCE

1 Havens, W. P., jun., and Paul, J. R., in *Viral and Rickettsial Infections of Man*, 3rd edition, 1959. J. B. Lippincott and Co., New York.

## NOTES AND COMMENTS

**Ribonucleic Acid Tablets.**—Dr. GEORGE X. TRIMBLE (Long Beach, California) writes: In the *Journal* ("Any Questions?" February 4, p. 374) a question appears concerning the merits of ribonucleic acid therapy for senile mental deterioration. Like the consultant, I had been unaware of any evidence indicating R.N.A. to be of value in this connexion. However, in a recent report[1] from a reputable mental centre evidence is presented indicating that R.N.A. therapy improved memory in ageing people. It should be of interest to see if further investigations confirm this work. Investigations on the relationship between memory and alteration of R.N.A. in neurons are being conducted by Dr. Holgar Hyden, of the University of Göteborg, who recently presented some of his findings at a University of California symposium on the control of the mind. Although Dr. Hyden's memory model has been described as proposing a "readily acceptable hypothesis" there is still a good deal of scepticism germane to its practical applicability.

OUR EXPERT replies: I have delayed replying to Dr. Trimble's comments until I had an opportunity of reading the article to which he refers. I am afraid that in spite of the fact that the report is from a reputable mental centre I find the evidence which the authors present in support of their claim that R.N.A. improves memory in ageing people and patients with cerebral arteriosclerosis entirely unconvincing. Part of their claim is based upon clinical impressions obtained from "relatives, friends, and the patient himself," and these are notoriously fallacious. The part of their evidence which is based on psychometric testing is also open to serious criticism and cannot be accepted as showing that R.N.A. has any effect on memory defect.

REFERENCE

1 Cameron, D. E., and Solyom, L., *Geriatrics*, 1961, **16**, 74.

**Treatment of Chloasma.**—Dr. H. J. KINGSLEY (Bulawayo, Southern Rhodesia) writes: I have often found the old treatment with chopras paint more effective and less risky than monobenzone ointment in chloasma.[1] Chopras paint is a lotion containing mercuric chloride 1 to 2 gr. (0.06–0.13 g.), bismuth subnitrate 10 gr. (0.65 g.), tragacanth powder 5 gr. (0.32 g.), water to 1 oz. (28 ml.); to be painted on the dark patches daily.

**Collected Articles from the "British Medical Journal"**

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

*Refresher Course for General Practitioners*, Volume 3 (26s. 9d.).

*Any Questions?*, Volume 3 (8s. 3d.).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7 Drumsheugh Gardens, Edinburgh.